American College of Clinical Pharmacy

1999 Annual Meeting
October 24-27, 1999

H. Roe Bartle Hall Convention Center
Kansas City Marriott Downtown Hotel
Kansas City, Missouri

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Adverse Drug Reactions/Drug Interactions

1. Analysis of adverse drug reactions in hospitalized patients. Mark A. Malek, Pharm.D., Dan E. Gelbard, M.D., Marc I. Gotthardt, M.D., Alegent Health Immanuel Medical Center, Omaha, NE.

PURPOSE: To analyze the incidence of adverse drug reactions in hospitalized patients over a 5-year period. The focus was on patients on multiple medications.

METHODS: Data from 494 reports over 5 years were reviewed. All reports met the hospital's definition of an adverse drug reaction. The reaction type, medication(s) involved, frequency, probability, and outcome classification were analyzed for each report.

RESULTS: Adverse reactions occurred in 1.72% of admissions during this period and 19.3% met the criteria for being preventable. Of 1367 drug reactions, the most common reason for being preventable (50.3%) was noncompliance and the most prevalent medication category was analgesics and antipyretics (33%). Analgesics and antipyretics were the most prevalent drug category for serious reactions (53%). The most frequent reaction type was dermatologic in nature (33%).

CONCLUSIONS: Although not a new finding, this study underscores the importance of adverse drug reactions in hospitalized patients and the need for better prescribing practices.


PURPOSE: To compare the incidence of adverse effects of enoxaparin in patients with normal renal function versus renal insufficiency.

METHODS: Data were retrospectively collected on any patient who received two or more doses of enoxaparin between March 1 and December 30, 1998. Charts were reviewed for demographics, renal function, and adverse effects. A major bleed was defined as a documented cerebrovascular, gastrointestinal, or retroperitoneal bleed, or drop in hemoglobin greater than 2 g/dl. Chi squared tests were performed for statistical analysis.

RESULTS: One hundred three patients were evaluated, 50 with normal renal function and 53 with renal insufficiency.

<table>
<thead>
<tr>
<th></th>
<th>Normal Renal Function</th>
<th>Renal Insufficiency</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=50</td>
<td>n=53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average age</td>
<td>64</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Average weight</td>
<td>85 kg</td>
<td>82 kg</td>
<td>NS</td>
</tr>
<tr>
<td>Percent male</td>
<td>56%</td>
<td>55%</td>
<td>NS</td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>10</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>1</td>
<td>16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total bleeds</td>
<td>11</td>
<td>27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2</td>
<td>9</td>
<td>&lt;0.05</td>
</tr>
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</table>

CONCLUSIONS: Patients receiving enoxaparin with renal insufficiency might be at a higher risk for bleeding complications, including death. The use of enoxaparin in patients with renal insufficiency should be discouraged, and heparin should be used.

Cardiology

3. Evidence-based appraisal of randomized, controlled trials in hypertension. Robin R. Feige, Pharm.D., Elaine Chiquette, Pharm.D., Kelly Montgomery, M.P.H.; University of Texas at Austin; University of Texas Health Science Center at San Antonio; Audie L. Murphy Memorial Veterans Hospital; San Antonio Cochrane Center, San Antonio, TX.

PURPOSE: To index the randomized, controlled trials (RCT) in the Cochrane Hypertension Review Group registry in order to facilitate future use and searches of the database.

METHODS: RCT were found through a comprehensive MEDLINE search (1966 to 1998) using a validated filter and MESH terms/text words to identify RCT related to hypertension. Data recorded from the abstracts included descriptors of intervention (length and type of therapy), setting (e.g., community, pregnancy, pre-operative), and outcome measures.

RESULTS: Of 4300 abstracts found by the search, 3700 have been reviewed to date. From the abstracts we identified 2620 definite randomized trials and 47 systematic reviews. More than half (85%) were of less than 6 months duration and only 5% followed patients for more than 1 year. The vast majority of trials assessed efficacy of drug therapy (80%). Diet, exercise, and salt restriction were utilized in less than 10% of trials. Most trials looked exclusively at blood pressure or physiologic effects (69%); a minority assessed antihypertensive intervention’s impact on cardiovascular endpoints (10%), quality of life (8%) or quality of life (2.4%). Most trials included middle aged men; other specific populations studied included elderly (9%), diabetes (3%), and severe hypertension (3%). Few trials included young adults with hypertension or subjects with multiple comorbidities.

CONCLUSIONS: Few RCT provide evidence to guide practitioners in long-term management of hypertension. Most trials focus on disease-oriented outcomes versus patient-oriented outcomes such as morbidity, mortality, or quality of life. Specific populations such as young adults and subjects with multiple risk factors deserve further study.

4. Platelet activity in vascular disease and the dose of aspirin. Robert L. Talbert, Pharm.D., Anne D. Leonard, B.S.N., Lesly A. Pearce, M.S., Robert G. Hart, M.D.; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; Axiom Research Corporation, Seattle, WA.

Antithrombotic trials with aspirin (ASA) using doses of 75-1500 mg/day have demonstrated a 25% reduction in vascular events in high-risk patients with no apparent relationship to dose (Cheat 1998;114 suppl:47S5). The national recommendation is ASA 50-325 mg/day for secondary prevention of vascular events.

PURPOSE: To determine if ASA dose differentially affects markers of platelet activity in elderly people with vascular disease.

METHODS: Patients receiving daily ASA for prevention of stroke or myocardial infarction due to atherosclerotic disease of the coronary or cerebral vessels were studied. Participants took buffered ASA 325 mg/day for 1 month, and then were randomly allocated to one of three ASA groups for 1 month. Participants took buffered ASA 325 mg/day for 1 month, and then were randomly allocated to one of three ASA groups for 1 month. Participants took buffered ASA 325 mg/day for 1 month, and then were randomly allocated to one of three ASA groups for 1 month.

RESULTS: DD, F1.2, DTXB2, and TXB2 were not different across the three groups at 4 weeks on ASA 325 mg. Median values (n=48) for DD, F1.2, DTXB2, and TXB2 were 138 ng/ml, 1.3 nM, and 124 pg/mg creatinine, respectively. Comparing values 4 weeks later (ANOVA-ranked differences), DD (p=0.009), DTXB2 (p=0.002), and TXB2 (p=0.001) were significantly affected by change in aspirin dose. Participants took buffered ASA 325 mg/day for 1 month, and then were randomly allocated to one of three ASA groups for 1 month.

CONCLUSIONS: These results suggest that ASA dosing affects platelet activity in elderly people with vascular disease.
5. \(\beta_2\)-adrenergic receptor polymorphisms and hypertension. Larisa M. Humma, Pharm.D., William F. Farmerie, Ph.D., Margaret A. Wallace, Ph.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: \(\beta_2\)-adrenergic receptor (\(\beta_2\AR\)) plays a role in blood pressure regulation by mediating peripheral vasodilation and plasma renin release. Polymorphisms of the \(\beta_2\AR\) gene commonly occur at codons 16 (Arg or Gly) and 27 (Gln or Glu), with the Gly16 and Gln27 forms displaying increased receptor down-regulation. The objective of this study was to determine if \(\beta_2\AR\) polymorphisms at codons 16 and 27 differ significantly between hypertensive subjects and published normotensive controls.

METHODS: Blood samples were collected from 67 hypertensive subjects for genotyping of the \(\beta_2\AR\). Following isolation of genomic DNA, \(\beta_2\AR\) genotype was determined by polymerase chain reaction and direct sequencing. \(\beta_2\AR\) genotypes and allele frequencies of hypertensive subjects were compared to those of 212 published normotensive controls (Liggett, et al. J Clin Invest 1998;102:1334-9).

RESULTS: The allele frequencies at codon 27 of the \(\beta_2\AR\) differed between hypertensives (Gln27 = 77%, Glu27 = 23%) and published normotensive controls (Gln27 = 58%, Glu27 = 42%), p<0.05. Hypertensives had a higher frequency of the homozygous Gln27 genotype than normotensives (Arg16 = 42%, Gly16 = 58% and normotensives (Arg16 = 38%, Gly16 = 62%).

CONCLUSION: This study suggests an association between \(\beta_2\AR\) polymorphism and hypertension. The Gln27 genotype may attenuate \(\beta_2\AR\)-mediated vasodilation in the periphery and contribute to the development of HTN.

6. Comparison between the efficacy and safety of simvastatin and atorvastatin. Kwok-Kin Mah, B.Sc. (Hons); Singapore General Hospital, Singapore.

PURPOSE: The study compared atorvastatin 10 mg and simvastatin 20 mg in patients with hypercholesterolemia or combined hyperlipidemia in terms of efficacy and safety.

METHODS: Medical records of 118 patients who had been on simvastatin monotherapy, and later switched to atorvastatin, were reviewed. Lipid profiles and liver function tests (LFT) results were documented.

RESULTS: Atorvastatin 10 mg produced a further drop in total cholesterol (-8.75%, p<0.005) and low-density lipoprotein cholesterol (LDL-cholesterol; -13.45%, p<0.005) when patients were switched from simvastatin 20 mg to atorvastatin 10 mg. High-density lipoprotein cholesterol (HDL-cholesterol) and triglyceride levels did not show any significant change. There was also no significant difference in alanine aminotransferase (ALT) levels when patients were switched from simvastatin 20 mg to atorvastatin 10 mg. No patients experienced elevation of ALT above 3 times the upper limit.

CONCLUSIONS: This study does not appear to be equipotent with simvastatin 20 mg.

7. The effects of controlled-onset extended-release verapamil on early morning rise in blood pressure and forearm vascular resistance. B. Nhi Nguyen, Pharm.D., Mohammad Noujidehi, Pharm.D., Robert B. Parker, Pharm.D., Jay M. Sullivan, M.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL; University of Tennessee, Memphis, TN; Trinity Mother Frances Hospital, Tyler, TX.

Controlled-onset extended-release verapamil (COER-V) is designed so that drug concentrations rise sharply in the early morning to coincide with the peak incidence of cardiovascular events. We studied the effects of COER-V on 24-hour ambulatory blood pressure (ABP), in particular the early morning rate of BP rise. We also compared the forearm vascular resistance (FVR) profile to those of controls and compared the effects of COER-V on the FVR diurnal pattern in hypertensives. Baseline 24-hour ABP was recorded and FVR was determined by venous occlusion plethysmography at 7 a.m., 2 p.m., and 9 p.m. in 19 untreated hypertensives. COER-V 380 mg was given at 9 a.m., and doses were titrated to achieve DBP ≤ 90 mm Hg. After 4 weeks on the final dose, 24-hour ABP and plethysmography studies were repeated and S-verapamil concentrations were determined over 24 hours by HPLC. COER-V reduced ABP throughout the 24-hour period (p<0.005) with significant differences found in the slopes of the early morning rise in BP, or change in systolic BP, in trough to peak and on drug (-8.75%, p<0.005) and low-density lipoprotein cholesterol (LDL-cholesterol; -13.45%, p<0.005) when patients were switched from simvastatin 20 mg to atorvastatin 10 mg. No significant differences were found in the slopes of the early morning rise in BP, or change in systolic BP, in trough to peak and on drug (+32/25 to 17/13 mm Hg), respectively. S-verapamil concentrations were higher at 7 a.m.: 41 ± 36 ng/ml. COER-V flattened the FVR curve although there were no significant differences at any single time point (baseline 7 a.m.: 58 ± 12, 4.5 ± 13, and 9.5 ± 11.5 mHg; 7a.m.: 55 ± 19 vs COER-V 7 a.m.: 51 ± 23, 7 p.m.: 51 ± 17, and 9 p.m.: 54 ± 17 mHg/min/100 g).

CONCLUSIONS: COER-V is an effective antihypertensive that lowers BP throughout a 24-hr period, but it does not blunt the early morning rise of BP risk despite peak S-verapamil concentrations in the early morning. The FVR diurnal pattern in hypertensives is different from normotensives. COER-V does not significantly alter the FVR diurnal pattern in hypertensives.

Published in Clin Pharmacol Ther 1999;65:130.
Cerivastatin (CER) is a synthetic HMG-CoA reductase inhibitor effective at microgram range.

PURPOSE: To compare the efficacy and safety of CER 0.3 and 0.4 mg to pravastatin (PRA) 20 and 40 mg.

METHODS: 1030 hypercholesterolemic patients were diet-stabilized for 6-8 weeks prior to randomization to CER 0.3 or 0.4 mg QD, or PRA 20 or 40 mg QD for 8 weeks. All patients were evaluated per protocol analysis. The primary comparison was reduction in LDL-C.

RESULTS: CER 0.3 and 0.4 mg reduced serum LDL-C to a significantly greater extent than PRA 20 and 40 mg, respectively. Results are expressed as mean (±SEM) percent change from baseline (mg/dl) to endpoint.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cerivastatin 0.3 mg</th>
<th>Pravastatin 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C BL</td>
<td>174 ± 2.4</td>
<td>172 ± 1.9</td>
</tr>
<tr>
<td>mean Δ</td>
<td>-29.6 ± 0.8*</td>
<td>-26.6 ± 0.7</td>
</tr>
<tr>
<td>Total-C BL</td>
<td>259 ± 2.7</td>
<td>258 ± 2.2</td>
</tr>
<tr>
<td>mean Δ</td>
<td>-20.5 ± 0.6*</td>
<td>-18.5 ± 0.6</td>
</tr>
<tr>
<td>LDL-C/HDLC BL</td>
<td>3.7 ± 0.1</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td>mean Δ</td>
<td>-32.0 ± 0.8</td>
<td>-31.1 ± 0.8</td>
</tr>
<tr>
<td>% of patients</td>
<td>53.0%</td>
<td>44.0%</td>
</tr>
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</table>

CONCLUSIONS: CER had greater efficacy than PRA in lowering serum LDL-cholesterol levels in hypercholesterolemic patients with no difference in safety.

11. Efficacy and safety of cerivastatin and pravastatin in the treatment of patients with primary hypercholesterolemia. Elijah Saunders, M.D., Keith Ferdinand, M.D., Laurence G. Yellen, Melvin J. Tonkon, M.D., Marcia Poland, M.S.; University of Maryland Medical Center, Baltimore, MD; Heartbeats Life Center, New Orleans, LA; Cardiology Associates Medical Group of East San Diego, San Diego, CA; Cardiology Associates Medical Group, Anaheim, CA; Smith-Kline Beecham, Collegeville, PA for the Cervinastatin Study Group.

PURPOSE: Cerivastatin, a member of the statin class of lipid-lowering agents, is currently available in the U.S. at dosages 0.3 mg, and 0.4 mg daily. This study compares the efficacy and safety of cerivastatin 0.3 mg QD to that of pravastatin 20 mg QD.

METHODS: In this randomized, double-blind, parallel group study across 28 centers, patients with primary hypercholesterolemia with and without documented coronary heart disease underwent 6-8 week dietary run-in prior to randomization to treatment with cerivastatin 0.3 mg or pravastatin 20 mg for 8 weeks. Plasma lipid profiles and safety measures were assessed.

RESULTS: Cerivastatin reduced LDL-C and total-C to a significantly greater extent than pravastatin. Presented as percent change (±SEM) from baseline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cerivastatin 0.3 mg</th>
<th>Pravastatin 20 mg</th>
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</thead>
<tbody>
<tr>
<td>LDL-C baseline</td>
<td>179.0 ± 2.0</td>
<td>172.3 ± 2.1</td>
</tr>
<tr>
<td>% Δ</td>
<td>-31.1 ± 0.8*</td>
<td>-26.0 ± 0.8</td>
</tr>
<tr>
<td>Total-C baseline</td>
<td>264.6 ± 2.2</td>
<td>258.2 ± 2.5</td>
</tr>
<tr>
<td>% Δ</td>
<td>-21.5 ± 0.6*</td>
<td>-17.8 ± 0.6</td>
</tr>
<tr>
<td>HDL-C baseline</td>
<td>50.9 ± 0.9</td>
<td>50.9 ± 0.9</td>
</tr>
<tr>
<td>% Δ</td>
<td>6.5 ± 0.8</td>
<td>4.7 ± 0.8</td>
</tr>
<tr>
<td>TG baseline</td>
<td>173.9 ± 4.5</td>
<td>175.2 ± 4.5</td>
</tr>
<tr>
<td>% Δ</td>
<td>-8.5 ± 1.7</td>
<td>-9.1 ± 1.7</td>
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CONCLUSIONS: Cerivastatin 0.3 mg and 0.4 mg reduced LDL-C and total-C to a significantly greater extent than pravastatin, presented as percent change (±SEM) from baseline.

12E. Pharmacological and non-pharmacological risk factors for hypertensive crisis. James E. Tisdale, Pharm.D., Neeta B. Amin, Pharm.D., Nagaraja Sharma, M.D., Howard Rosman, M.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: To determine the incidence of haloperidol (H)-induced QTc interval prolongation in critically ill patients, and to test the hypothesis that H-induced QTc interval prolongation is related to dose, pretreatment QTc interval, female sex, and/or history of ischemic heart disease.

METHODS: This was a retrospective case-controlled study of 215 critically ill patients with pretreatment QTc interval > 450 ms who received intravenous H for agitation. Patients were excluded if they had other metabolic, pharmacological, or neurological risk factors for QTc prolongation, defined as on-treatment QTc > 450 ms. Demographics, comorbid conditions, H dose, and QTc intervals were compared in patients who developed QTc prolongation vs those who did not.

RESULTS: QTc prolongation developed in 107 (49.8%) patients. By univariate analysis, longer pretreatment QTc interval (p<0.003), higher H dose within 24 hours prior to maximum QTc (p=0.0003), higher total H dose (p<0.001), and longer duration of therapy (p<0.03) were risk factors.

CONCLUSIONS: QTc interval prolongation associated with intravenous H occurs frequently in critically ill patients. Longer pretreatment QTc interval is a risk factor for H-induced QTc interval prolongation. Published in Clin Pharmacol Ther 1999;65:130.

13E. Risk factors for QTc interval prolongation induced by intravenous haloperidol. James E. Tisdale, Pharm.D., Neeta B. Amin, Pharm.D., Nagaraja Sharma, M.D., Howard Rosman, M.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: To compare the efficacy of CER 0.4 mg to CER 0.3 mg or fluvastatin 40 mg (FLUV).

METHODS: In this double-blind, multicenter trial, 908 hypercholesterolemic patients underwent 10 week lipid stabilization before randomization to treatment with CER 0.3 mg or 0.4 mg or 8-week treatment with placebo, then FLUV, all given QD.

RESULTS: CER 0.4 mg was more effective than FLUV in reducing LDL-C, total-C, and triglycerides (TRIG), and in elevating HDL-C. Results are expressed as mean percent change from baseline to endpoint.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cerivastatin 0.3 mg</th>
<th>Pravastatin 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C baseline</td>
<td>191.8 ± 16.7</td>
<td>191.7 ± 19.1</td>
</tr>
<tr>
<td>% change</td>
<td>-30.8*</td>
<td>-23.5*</td>
</tr>
<tr>
<td>Total-C</td>
<td>-21.5*</td>
<td>-23.5*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>7.8*</td>
<td>8.1*</td>
</tr>
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</table>

CONCLUSIONS: ED visits for hypertensive crisis are associated with prior heart failure and less well-controlled hypertension. Therapy with β-blockers, diuretics, or calcium channel blockers is associated with a reduced risk of HC, while clonidine therapy is associated with an increased risk.

Published in Clin Pharmacol Ther 1999;65:130.
Both drugs were well-tolerated. Myalgia occurred in ≤5% of both treatment groups. Discontinuations due to adverse events were similar (≤7%). CK elevations >20× upper limits of normal (ULN) occurred in ≤3% of patients per group. Incidence of elevated plasma transaminase levels (>3× ULN) were also similar (range 0-2.2%).

CONCLUSIONS: CER produces greater LDL-C lowering (-33%) than FLUV (-23%) at 1% of daily dose with no added safety concerns.

15. Reduction in major bleeding and length of hospitalization following percutaneous coronary intervention with abciximab: impact of a targeted clinical pharmacy education program. Paul P. Dobesh, Pharm.D., BCPS, Jonathan E. Lakamp, Pharm.D., BCPS; St. Louis College of Pharmacy; St. Luke's Hospital, St. Louis, MO.

PURPOSE: Controlled clinical trials have demonstrated that weight-adjusted heparin dosing, early sheath removal, and avoidance of post-procedure heparin can reduce the incidence of bleeding in patients undergoing percutaneous coronary interventions (PCI) with abciximab. We evaluated the impact of a clinical pharmacy education program on steps to minimize bleeding complications identified by clinical pharmacists and presented to invasive cardiologists and nursing staff in a 493-bed community hospital. Bleeding rates, adherence to weight-adjusted heparin dosing recommendations, time of sheath removal, post-procedure heparin use, and length of hospitalization (LOH) were compared retrospectively in patients undergoing PCI with abciximab before (5/97-4/98; n=28) and after (6/98-11/98; n=65) presentation of the educational program.

RESULTS: Compared to the pre-education period, patients receiving PCI with abciximab after presentation of the educational program displayed a decreased incidence of major bleeding (1.8% vs 14.3%; p=0.042), shorter median indwelling sheath time (7.5h vs 13h; p=0.011), reduced post-PCI heparin use (20% vs 82%; p<0.001) and reduced median LOH (2.0 vs 4.5 days; p<0.001). Adherence to weight-adjusted heparin recommendations did not improve significantly in the post-education period (29% vs 38%; p=NS).

CONCLUSIONS: A clinical pharmacy education program targeted toward invasive cardiologists and cardiology staff can reduce bleeding complications and LOH in patients undergoing PCI.

16. Outcomes of abciximab use in patients undergoing percutaneous coronary intervention: preliminary results in the community hospital setting. Paul P. Dobesh, Pharm.D., BCPS, Jonathan E. Lakamp, Pharm.D., BCPS; St. Louis College of Pharmacy; St. Luke's Hospital, St. Louis, MO.

PURPOSE: Controlled clinical trials have shown significant reductions in the composite of death and myocardial infarction (MI) following the use of abciximab in patients undergoing percutaneous coronary intervention (PCI). It is not known if similar results can be achieved outside of large controlled studies conducted primarily in the tertiary care environment. We evaluated our institution’s initial experiences with the use of abciximab in patients undergoing PCI to determine the relative success of this therapy in the community hospital setting.

METHODS: Medical records were reviewed and telephone follow-up was conducted with 83 patients who underwent PCI (48 MI, 26 unstable angina, and 9 stable angina) with abciximab at our facility between May 1997 and November 1998. Occurrence of death/MI at 30 days and 6 months post-PCI were recorded. These data were compared (chi squared analysis) with published results obtained from major controlled trials with abciximab.

RESULTS: Comparison of death/MI at 30 days (p=0.106) and 6 months (p=0.038) post-PCI revealed no significant difference between our community hospital and the published clinical trials.

CONCLUSIONS: Initial experiences with the use of abciximab in patients undergoing PCI in our institution suggest that results comparable to those obtained in controlled trials can be achieved in the community hospital setting. Once a larger number of patients have been treated, subsequent re-evaluation of this experience will be necessary to confirm these findings with greater confidence.


PURPOSE: This study compared sequential versus simultaneous intravenous combination diuretic therapy to determine if sequence of administration is a factor in removing fluid from congestive heart failure patients.

METHODS: The study was an open label, randomized, crossover pilot study. Efficacy was primarily assessed through measurement of urine sodium excretion over 6 hours. Secondary measures included urine potassium excretion over six hours, total inputs and outputs over 6 and 24 hours, changes in blood urea nitrogen and serum creatinine.

RESULTS: Of the nine patients enrolled in the study, seven patients were evaluated. The remaining two were not evaluated because they received only one treatment. With regard to urine sodium excretion over six hours, five of the seven patients demonstrated a better response from simultaneous rather than sequential therapy. Average sequential sodium excretion over six hours was 175.3 mEq versus 129.8 mEq for sequential dosing. Net fluid loss at both six and twenty-four hours favored simultaneous dosing. With regard to change in weight and change in blood urea nitrogen and serum creatinine, there appeared to be no difference between simultaneous versus sequential dosing.

CONCLUSIONS: These data suggest it may be more beneficial to administer intravenous combination diuretic therapy simultaneously rather than sequentially. Further data collection is needed with a larger sample size to determine significance.

18E. Cytochrome P450 induction improves endothelial dysfunction in insulin resistance. Frasad V.G. Katakam, M.D., Ph.D., Michael R. Ujhelyi, Pharm.D., Allison W. Miller, Pharm.D.; University of Georgia; Medical College of Georgia School of Medicine; Augusta VA Medical Center, Augusta, Georgia.

PURPOSE: Impaired endothelium dependent relaxation in insulin resistant (IR) rats is due to a defect in endothelium derived hyperpolarizing factor (EDHF). EDHF may be a by-product of cytochrome-P450 (CP) metabolism. Hence increased CP activity may correct the IR induced EDHF defect.

METHODS: Rats were randomized to control (C; n=32) and IR (n=32). Each group was further randomized to treatment (n=48) or placebo (n=16). CP inhibition and induction was achieved by miconazole (Mic; 3 day) and phenobarbital (PB; 3 and 14 days). Blood pressure (BP) and in vitro vascular function was assessed. Specifically, in small mesenteric arteries, acetylcholine (ACh) and EDHF mediated relaxation were determined.

RESULTS: Both 3 and 14 day treatment of PB improved ACh induced Emax from 44 ± 4% for placebo to 70 ± 7% and 88 ± 3% after 3 and 14 days, respectively (p<0.05). In addition, 3 and 14 day PB improved EDHF mediated relaxation from 12 ± 2% for placebo to 40 ± 4% for day 3 and 59 ± 9% for day 14 (p<0.05). Also, 14 day PB normalized the BP in IR rats. PB did not affect C. Mic reduced maximal relaxation (Emax) to ACh in C (67 ± 8% in Mic vs 92 ± 4% in placebo, p<0.05). Similarly, EDHF mediated relaxation was reduced in Mic treated C. Mic also induced an elevation of BP in C. Mic did not affect IR.


PURPOSE: Atrial fibrillation (AF) is a common complication following CABG surgery. The outcome of 275 episodes of post-CABG AF ≥ 1 hr duration treated with a beta-blocker (BB) or a calcium channel antagonist (CA) was evaluated.

METHODS: A retrospective chart review of 431 consecutive CABG and 50 valve implant surgeries was conducted. Two hundred seventy-five episodes of AF ≥ 1 hr were treated with a BB or a CA with or without baseline digoxin (DIG) therapy. Success was defined as cardioversion (CV) to sinus rhythm or heart rate control (HRC) < 90 bpm. Time to success was also recorded as a primary outcome parameter.

RESULTS: One hundred sixty episodes of AF were treated with BB (72 = esmolol; 28 = IV metoprolol; 60 = PO metoprolol) and 115 episodes of AF were treated with CA (58 = IV diltiazem; 32 = PO diltiazem; 25 PO = verapamil). Baseline DIG therapy was equally distributed between the BB and CA treatment groups. BB had significantly greater success than CA (81% vs 54%; p=0.03). Baseline DIG therapy did not influence results. Time to CV or HRC was significantly shorter with esmolol than with other BB or any CA. Incidences of hypotension, bradycardia, heart block, and heart failure were not different between BB and CA.

CONCLUSIONS: BB are superior to CA for post-CABG AF management. IV esmolol is associated with the shortest time to successful treatment. BB remain the drugs of choice for prevention and treatment of post-CABG AF.

PHARMACOTHERAPY Volume 19, Number 10, 1999


PURPOSE: This study was conducted to determine if there was a difference in the commonly accepted clinical indicators of reperfusion (resolution of ST segment elevation and chest pain [CP]) between those patients who received either alteplase or rt-PA.

METHODS: This was a retrospective study evaluating patients at our institution who received either alteplase or rt-PA in 1998. Data was collected for demographics; comorbidities; aspirin use; specific thrombolytic administered; site of myocardial infarction; time of evidence of reperfusion (resolution of ST segment elevation or partial resolution to a persistent small elevation and/or CP); time of evidence of reocclusion (EGC changes and/or recurrent CP); and emergent interventions (i.e., intra-arterial balloon pump placement or emergent transfer). Logistic regression analysis (STATISTIX®) was performed using a maximum likelihood function. Odds ratios with 95% confidence intervals were calculated.

RESULTS: A total of 90 patients were evaluated (44 received alteplase, 46 received rt-PA). There were no differences between the groups (p>0.05) regarding age, gender, site of infarct, number of comorbidities, or time to treatment. Logistic regression analysis found all variables to be necessary for a good fitting model, but only the thrombolytic had any predictive value for an adverse event (lack of reperfusion or reocclusion). The odds ratio (95% CI) for reperfusion was 3.83 (1.13, 12.95). This increased risk was associated with previous CVA/stroke.

CONCLUSION: Based on the results of this analysis, we are discouraging the use of a single formulary agent for all thrombolytic eligible patients, and encouraging the use of alteplase for younger males.


PURPOSE: To compare the predictive performance of a fluorescence polarization immunoassay (TDX Digoxin), and radioimmunoassay (RIA, Kallestad Labs) with low-pressure liquid chromatography/RIA (LPLC/RIA, Longerich, et al) digoxin assay, which removes digoxin-like immunoreactive substances (DLIS). Previously, older RIAs and FRIs have been shown to overpredict serum digoxin concentrations (SDC) in patients with renal dysfunction secondary to assay interference with DLIS. Whether this occurs with newer assay versions is unknown.

METHODS: Prospective study designed to determine the predictive performance (Sheiner and Beal) of using TDX and RIA, compared to LPLC/RIA digoxin assay in those patients who received digoxin in a clinical setting. The local normal range for TDX, RIA, and LPLC/RIA were 0.5-2.0 ng/ml, 0.4-2.0 ng/ml, and 0.45-2.1 ng/ml, respectively. The local normal range for SDC were 0.6-2.0 ng/ml, 0.5-2.0 ng/ml, and 0.6-2.0 ng/ml, respectively. The magnitude of bias (measured in % ME and precision (measured in % SDE)) was calculated with 95% confidence limits (CI). The magnitude of bias was calculated by dividing the mean error of the compared assay by the mean SDC measured by the reference standard, LPLC/RIA.

RESULTS: Bias for each group was determined.

<table>
<thead>
<tr>
<th>Number of Magnitude</th>
<th>Group</th>
<th>Digoxin Assay</th>
<th>Number of</th>
<th>ME</th>
<th>CI</th>
<th>Bias</th>
<th>Group</th>
<th>Magnitude</th>
<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDX digoxin II</td>
<td>97</td>
<td>-0.1610 (-0.2484, -0.0735)</td>
<td>13.56%</td>
<td>4.98%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIA</td>
<td>96</td>
<td>-0.0638 (-1.0164, 0.0289)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group II</td>
<td>TDX digoxin II</td>
<td>89</td>
<td>0.3002 (0.1084, 0.4921)</td>
<td>8.41%</td>
<td>8.36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIA</td>
<td>89</td>
<td>-0.2987 (-0.4528, -0.1445)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group III</td>
<td>TDX digoxin II</td>
<td>90</td>
<td>-0.3992 (-0.5977, -0.2008)</td>
<td>5.74%</td>
<td>2.27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIA</td>
<td>90</td>
<td>-0.4685 (-0.6300, -0.3439)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

With regard to precision, both assays were imprecise for all groups.

CONCLUSION: Overall, RIA and TDX were biased to overpredict SDC in patients with renal dysfunction; however, the magnitude of bias was low (<20%) for both assays in all groups. Since both RIA and TDX are easier to perform than LPLC/RIA, either assay may be used to measure SDC in patients with renal dysfunction.


PURPOSE: This study examined the economic impact of inotropic agent selection in patients successfully bridged to heart transplant in 1993 and 1996 at our center.
ACCP 1999 ANNUAL MEETING ABSTRACTS

METHODS: Three treatment groups were identified from itemized billing records: milrinone (n=48), dobutamine (n=46), and combined dobutamine plus amrinone milrinone (n=46). Costs (1997 U.S. $) were calculated for each billed item using institutional cost:charge ratios, excluding professional fees. Pretransplant (preHT) and posttransplant (postHT) costs were categorized by pharmacy, procedure, lab, bed, blood product, respiratory care, and supply. Per diem costs (cost/day) were calculated to adjust for varying length of stay.

RESULTS: No intergroup baseline demographic or clinical differences were observed. Categorized cost comparisons are:

<table>
<thead>
<tr>
<th>PreHT Per Diem Cost</th>
<th>Milrinone</th>
<th>Dobutamine</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>$246 ± 623</td>
<td>$2451 ± 484</td>
<td>$2742 ± 838</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>425 ± 61⁴</td>
<td>48 ± 103⁴</td>
<td>188 ± 84⁴</td>
</tr>
<tr>
<td>Procedure</td>
<td>154 ± 233</td>
<td>282 ± 247</td>
<td>366 ± 484</td>
</tr>
<tr>
<td>Lab</td>
<td>226 ± 122</td>
<td>296 ± 156</td>
<td>360 ± 129</td>
</tr>
<tr>
<td>Bed</td>
<td>1014 ± 53</td>
<td>978 ± 103</td>
<td>1015 ± 44</td>
</tr>
</tbody>
</table>

⁎⁎ like letters differ, p<0.02

Other preHT costs were minor and did not differ between groups. No differences in categorized costs were observed postHT.

CONCLUSION: Use of a milrinone-based inotropic strategy led to nonsignificant increases in total per diem costs in patients successfully bridged to transplant. Greater pharmacy costs of milrinone appear to be partially offset by reduced procedure and laboratory costs. Formulary decisions on inotropic therapy should not be based solely on drug acquisition costs.

Presented at the 3rd Annual Scientific Meeting of the Heart Failure Society of America, San Francisco, CA, September 23, 1999.

26. Practice patterns versus clinical trial use of the newer glycoprotein IIb/IIIa inhibitors

Anne Spencer, Pharm.D., BCPS, Jean Nappi, Pharm.D., BCPS, FCCP; Medical University of South Carolina, Charleston, SC.

PURPOSE: To document the clinical use of eptifibatide (E) and tirofiban (T) in a tertiary care setting.

METHODS: Patients receiving either E or T were identified at the initiation of therapy. Patient demographic information, drug, dose, duration of infusion, incidence of bleeding, thrombocytopenia, heparin administration, emergent revascularization, and cost data were collected prospectively.

RESULTS: Thirty-seven cases of E and T administration between November 1, 1998 and May 31, 1999 were included in this evaluation.

CONCLUSION: E and T are used in clinical practice in a similar manner to clinical trial reports. A prospective study is warranted.


Cerivastatin Study Group.

PURPOSE: To test the hypothesis of whether MIS (200 µg BID) plus D (10 mg BID) produced a significantly greater reduction in LDL-C than D alone.

METHODS: In this randomized, double-blind, trial, 1170 hypercholesterolemic patients underwent 10-week diet stabilization prior to 8-week treatment with CER 0.4 or 0.8 mg QD, or placebo.

RESULTS: CER 0.4 mg produced a significantly greater LDL-C reduction than D alone. The NCEP goal of 130 mg/dl (no CAD, ≥ 2 risk factors) was reached with CER 0.8 mg by 78% of patients.

CONCLUSION: CER 0.8 mg produced a significantly greater LDL-C reduction than CER 0.4 mg. CER 0.8 mg reduced TG by 28% in 106 patients with basal TG > 250 mg/dl. Results are expressed as mean percentage change (± SEM) from baseline (± mg/dl) to 8-week endpoint.

Lipid Parameters

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo (n=177)</th>
<th>CER 0.4 (n=168)</th>
<th>CER 0.8 (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>185 ± 41</td>
<td>101 ± 21</td>
<td>100 ± 36</td>
</tr>
<tr>
<td>HDL-C</td>
<td>41 ± 8</td>
<td>53 ± 17</td>
<td>52 ± 18</td>
</tr>
<tr>
<td>TG</td>
<td>154 ± 234</td>
<td>282 ± 247</td>
<td>260 ± 129</td>
</tr>
</tbody>
</table>

CONCLUSION: MIS produced a significantly greater LDL-C reduction than placebo. CER 0.8 mg reduced TG by 28% in 106 patients with basal TG > 250 mg/dl. Results are expressed as mean percentage change (± SEM) from baseline (± mg/dl) to 8-week endpoint.

Causes of AE with rates > 5% and discontinuations were similar across groups. CK levels > 10x upper limits of normal with myalgia occurred in 0.5%, and 0.5% of patients receiving placebo, CER 0.4 or 0.8 mg. CONCLUSION: CER 0.8 mg produced a significantly greater LDL-C reduction than CER 0.4 mg. The NCEP goal of 130 mg/dl (no CAD, ≥ 2 risk factors) was reached with CER 0.8 mg by 78% of patients.

29. Does misoprostol attenuate NSAID-induced changes in blood pressure and renal hemodynamics?: the MEDIC study.

PURPOSE: To compare the efficacy and safety of CER 0.8 mg to CER 0.4 mg or placebo.

METHODS: In this randomized, double-blind trial, 1170 hypercholesterolemic patients underwent 10-week diet stabilization prior to 8-week treatment with CER 0.8 or 0.4 mg QD, or placebo.

RESULTS: CER 0.8 mg produced a significantly greater LDL-C reduction than CER 0.4 mg. The NCEP goal of 130 mg/dl (no CAD, ≥ 2 risk factors) was reached with CER 0.8 mg by 78% of patients.

CONCLUSION: CER 0.8 mg produced a significantly greater LDL-C reduction than CER 0.4 mg. CER 0.8 mg reduced TG by 28% in 106 patients with basal TG > 250 mg/dl. Results are expressed as mean percentage change (± SEM) from baseline (± mg/dl) to 8-week endpoint.

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CONCLUSION: MIS produced a significantly greater LDL-C reduction than placebo. CER 0.8 mg reduced TG by 28% in 106 patients with basal TG > 250 mg/dl. Results are expressed as mean percentage change (± SEM) from baseline (± mg/dl) to 8-week endpoint.

Causes of AE with rates > 5% and discontinuations were similar across groups. CK levels > 10x upper limits of normal with myalgia occurred in 0.5%, and 0.5% of patients receiving placebo, CER 0.4 or 0.8 mg. CONCLUSION: CER 0.8 mg produced a significantly greater LDL-C reduction than CER 0.4 mg. The NCEP goal of 130 mg/dl (no CAD, ≥ 2 risk factors) was reached with CER 0.8 mg by 78% of patients.

29. Does misoprostol attenuate NSAID-induced changes in blood pressure and renal hemodynamics?: the MEDIC study.

PURPOSE: To test the hypothesis of whether MIS (200 µg BID) plus D (10 mg BID) attenuates D-induced increased BP loads and renal hemodynamic changes we conducted a prospective, double-blind, randomized, 14-day crossover design study in salt-sensitive elderly subjects with stage I-II hypertension. Salt sensitivity was determined by a randomized, 14-day crossover design study in salt-sensitive elderly subjects.

METHODS: To test the hypothesis of whether MIS (200 µg BID) plus D (10 mg BID) attenuates D-induced increased BP loads and renal hemodynamic changes we conducted a prospective, double-blind, randomized, 14-day crossover design study in salt-sensitive elderly subjects with stage I-II hypertension. Salt sensitivity was determined by a randomized, 14-day crossover design study in salt-sensitive elderly subjects.

METHODS: To test the hypothesis of whether MIS (200 µg BID) plus D (10 mg BID) attenuates D-induced increased BP loads and renal hemodynamic changes we conducted a prospective, double-blind, randomized, 14-day crossover design study in salt-sensitive elderly subjects with stage I-II hypertension. Salt sensitivity was determined by a randomized, 14-day crossover design study in salt-sensitive elderly subjects.
30. A retrospective evaluation of discharge medications in post-myocardial infarction patients. Brigitte T. Luong, Pharm.D., Wendy C. Cox, Pharm.D., Jean Napi, Pharm.D., FCP, BCPS. Medical University of South Carolina, Charleston, SC.

PURPOSE: Discharge medications of post-myocardial infarction (MI) patients at an academic hospital were evaluated for compliance with the American College of Cardiology/American Heart Association’s (ACC/AHA) Guidelines for the Management of Patients with Acute MI. METHODS: The medical records of 90 acute MI survivors discharged between March 1, 1997 and February 28, 1999 were reviewed. Patients’ discharge medications (antiplatelet agent, beta-blocker, angiotensin converting enzyme [ACE] inhibitor, lipid-lowering agent, and sublingual nitroglycerin) were recorded, as well as relative or absolute contraindications if the agents were not prescribed. RESULTS: Antiplatelet agents, beta-blockers, ACE inhibitors, lipid-lowering agents, and sublingual nitroglycerin were prescribed in 93.3%, 60%, 52.2%, 53.3%, and 47.7% of the patients, respectively. Of the patients not prescribed these agents and without relative or absolute contraindications, 3.3%, 10%, 8.8%, 32.2%, and 43.3% were not prescribed an antiplatelet agent, beta-blocker, ACE inhibitor, lipid-lowering agent, or sublingual nitroglycerin, respectively. CONCLUSION: The percentage of patients prescribed the agents recommended in the ACC/AHA guidelines was above those found in the literature after adjusting for relative or absolute contraindications. Areas for improvement include the prescribing of lipid-lowering agents and sublingual nitroglycerin.

31. Meta-analysis of the antihypertrophic effects of prophylactic amiodarone following cardiac surgery. Paul E. Nolan, Jr., Pharm.D., James E. Tisdale, Pharm.D., Margaret E. McGuinness, Pharm.D., K. Slack, Ph.D., for the Meta-Analysis Pharmacy Collaborators for Amiodarone and Sotalol Investigators; University of Arizona, Tucson, AZ; Wayne State University, Detroit, MI; Philadelphia College of Pharmacy, Philadelphia, PA; Creighton University, Omaha, NE.

PURPOSE: This study evaluated the efficacy and safety of intravenous (IV) or oral (PO) amiodarone (AM) administered prophylactically to decrease atrial fibrillation (AF) following cardiac surgery (CS).

METHODS: This meta-analysis compared the effects of prophylactic AM, six prospective, randomized, controlled studies comparing either IV or PO AM (n=484) vs placebo (PL; n=14) were aggregated using standard meta-analytic techniques. RESULTS: There were no significant differences between the AM and PL groups with respect to age, gender, left ventricular ejection fraction, total, aortic cross-clamp time, number of coronary artery bypass grafts or pre-CS AF. Occurrence of post-CS AF was significantly reduced by AM: 26% vs 36% (OR: 0.61; 95% CI: 0.46-0.81; p=0.001). The impact of prophylactic AM with respect to length of stay (LOS) was decreased from 143.5 mg/dl to 105.2 mg/dl. This drop was statistically significant (p=0.012). For the experimental group, LDL-cholesterol decreased from 108.5 mg/dl to 104.8 mg/dl. This drop was statistically significant (p<0.002).

CONCLUSION: Based on our preliminary results, the percent reduction in LDL is similar in every day and every other day dosing with atorvastatin. Every other day dosing should not result in significant drug cost savings without compromising the therapeutic effects.


PURPOSE: Although scientific evidence indicates that aspirin significantly impacts the clinical outcomes of post-myocardial infarction (MI) patients, the optimum dose remains controversial. We evaluated the effect of aspirin dose on outcomes in post-MI patients.

METHODS: The records of 534 post-MI patients discharged from our institution from June 1996 to May 1997 were reviewed and demographic, clinical, laboratory and pharmacy data were collected. Aspirin dose on discharge was categorized as low (<160 mg daily) or standard (≥160 mg daily), based on AHA/ACC guidelines. Subsequent cardiovascular events, including reinfarction, unstable angina and cardiac interventions or death, were assessed at 6 months post discharge. The impact of aspirin dose on the likelihood of an event occurring within 6 months was analyzed using univariate and stepwise multiple logistic regression.

RESULTS: Of the 491 patients with complete follow-up data, aspirin was prescribed in 87% of the patients. 79% received the standard dose and 8% received low dose aspirin. Events were documented in 22% of the patients. Compared to no aspirin, treatment with low dose was not associated with a decrease in event rate (OR 1.25; 95% CI 0.53-2.97, p=0.61). Standard dose aspirin was associated with a decrease in event rate (OR 0.59; 95% CI 0.31-0.82, p=0.004) and remained significant in multivariate analysis (OR 0.55; 95% CI 0.33-0.92, p=0.02).

CONCLUSION: Although a small number of patients were treated with low dose aspirin, our data indicate that it had no significant impact on outcomes while standard dose aspirin was associated with improved outcomes. This illustrates the need to increase awareness of optimal aspirin dosing in the medical management of post-MI patients.

34. Post-myocardial medication use and outcomes in patients at a Veterans Affairs medical center. Margaret E. McGuinness, Pharm.D., Madeline Downey, Pharm.D.; Oregon State University; Legacy Health System–Mt. Hood Community Hospital, Gresham, OR.

PURPOSE: Myocardial infarction (MI) remains a leading cause of death. Post-MI therapy with beta blockers (BB), aspirin, and angiotensin converting enzyme inhibitors (ACEI) reduce mortality. The purpose of this study conducted in a Veterans Affairs medical center (VA) was to evaluate medication prescription of BB, ACEI and aspirin in patients discharged following MI, identify documentation of contraindications for non-drug use, and patient outcomes.

METHODS: Patients identified by ICD-9 codes for MI who were treated and discharged from the VA between January 1995 and December 1996 were evaluated for discharge medications, and reinfarction and mortality rates, during follow up through April 1998. Documentation of contraindications to drug therapy were also recorded. Pharmacy medication records and patient medical records were used as data source.

RESULTS: The average age of the 283 eligible patients was 64 years (99.7% male). At discharge 76% were on BB, 51% on ACEI (60% [35/58]; patients with EF <40%); and 98% on aspirin. Documented contraindications to therapies were found for 72% BB, 36% ACEI, (46% with EF <40%); and 98% aspirin. Reasons for non-use of BB were primarily cardiac (44%; 67% CHF); and respiratory (54%, 85% COPD); and for ACEI, renal (54%). Reinfarctions occurred in 32% of patients, and overall mortality was 7% during median follow up of 22 months.

CONCLUSIONS: Post-myocardial medical management with BB and ACEI and documentation of contraindications to therapies is not optimal. Advocacy of recommended therapies and improved documentation of contraindications for non drug use needs to be facilitated.


PURPOSE: Ambulatory blood pressure monitoring (ABPM) better represents blood pressure (BP) than an office measure, but is time-intensive and costly. We correlated home blood pressure monitoring (HBPM) to ABPM, and the meaningful ability of each to predict the other.

METHODS: Patients from two managed care organizations deemed hypertensive or white coat hypertensive by their physician were enrolled.
Patients monitored their home BP 2-3 times daily for 2 weeks at defined intervals using a digital automatic home BP monitor. ABPM was performed within 24 hours of the last HBPM recording. The last BP measurement before the first ABPM recording (% of readings > 140/90 mm Hg) was compared. Percent of patients requiring treatment, defined as a BP load ≥40%, was also compared.

RESULTS: Two hundred eight patients were enrolled and 166 (54 ± 11 years, 43% male) had complete data. The mean systolic/diastolic BP at baseline was 132 ± 15 mm Hg/97 ± 11 mm Hg for HBPM, and 138 ± 14 mm Hg/83 ± 10 mm Hg for ABPM (p<0.03 for both SBP and DBP). The mean systolic/diastolic load was 32 ± 32/21 ± 27% for HBPM, and 43 ± 33/28 ± 27% for ABPM (p<0.001 for both SBP and DBP). HBPM identified 40% requiring therapy versus 50% with ABPM. There was no difference in the identification of patients requiring treatment between monitors (p=0.078).

CONCLUSIONS: There was a significant BP difference between HBPM and ABPM; however, there was no difference in the percent of patients requiring treatment.

36. Lidocaine widens the window of vulnerability to monophasic, but not biphasic T-wave shocks. J. Jason Sims, Pharm.D., Allison W. Miller, Pharm.D., Michael R. Uhjelyi, Pharm.D.; University of Georgia; Medical College of Georgia; Augusta VA Medical Center, Augusta, GA.

PURPOSE: Implantable defibrillators decrease sudden cardiac death mortality, but are limited by the energy required to defibrillate (i.e., high DER values). Multiple drugs increase DER values and cause failed defibrillation, but the specific mechanisms are unknown. One hypothesis of defibrillation relates to shock proarrhythmia, where the less proarrhythmic a shock the lower the DER value. Since defibrillation shocks induce ventricular fibrillation (VF), we determined during a vulnerable window of ventricular repolarization (T-wave shocks), our purpose was to determine if lidocaine, a model drug probe, widens the window of myocardial vulnerability to T-wave shocks.

METHODS: Window of myocardial vulnerability was assessed for monophasic (MS) and biphasic (BS) T-wave shocks by determining the shortest and longest coupling intervals (CI) that induced VF. Twenty-four swine were randomized to four groups: MS/lidocaine, MS/placebo, BS/lidocaine, or BS/placebo. Shocks of increasing voltage were delivered during a range of CI (140-320 ms) until 600 volts was reached or VF was induced. Window of vulnerability and DER values were determined at baseline and during lidocaine 7.5 mg/kg/hr or placebo.

RESULTS: The table below shows the window of myocardial vulnerability for the MS/lidocaine and BS/lidocaine groups. Lidocaine did not alter the shortest CI that a MS induced VF, but increased the longest CI by 22 ± 8 ms (p<0.03) and 26 ± 8 ms (p<0.02), respectively. Thus, the BS window of vulnerability did not change. Also, lidocaine increased DER values for MS from 12 ± 2 J to 16 ± 2 J (p<0.008), but did not alter BS DER values.

Placebo did not alter any parameter.

<table>
<thead>
<tr>
<th>Base</th>
<th>Lido</th>
<th>Base</th>
<th>Lido</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>DER</td>
<td>CI</td>
<td>DER</td>
</tr>
<tr>
<td>12 ± 2</td>
<td>5 ± 2*</td>
<td>14 ± 1</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>10 ± 2</td>
<td>6 ± 2*</td>
<td>12 ± 2</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>8 ± 1</td>
<td>4 ± 2*</td>
<td>9 ± 1</td>
<td>12 ± 1</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Lidocaine widens the MS window of vulnerability by prolonging only the longest point of repolarization (CI) where VF is induced. Lidocaine shifts the BS window of vulnerability to longer coupling intervals, but does not widen it. The larger MS vulnerable window produced by lidocaine may impair MS defibrillation because the shock is more likely to be delivered within the vulnerable window during fibrillation.

37E. Myocardial vulnerability to ventricular fibrillation is regulated by dispersion in conduction, but not dispersion in refractoriness. J. Jason Sims, Pharm.D., Allison W. Miller, Pharm.D., Michael R. Uhjelyi, Pharm.D.; University of Georgia; Medical College of Georgia; Augusta VA Medical Center, Augusta, GA.

PURPOSE: Acute myocardial ischemia increases myocardial vulnerability to ventricular fibrillation (VF). Myocardial vulnerability is caused by myocardial electrical heterogeneity. However, it is unclear whether dispersion in conduction velocity or refractoriness is responsible. We determined the effects of dispersion in conduction velocity and refractoriness on VF thresholds (VFT).

METHODS: Male Sprague-Dawley rats were assigned to burn (n=10) or sham (n=10) groups, anesthetized, and underwent laparotomy during which the proximal jejunum was cannulated. The segment was perfused with buffer containing 4H-propranolol. The burn group underwent a 30% TBSA full thickness burn 24 hours prior to the intestinal perfusion. Perfusate samples were assayed for TNF-α, IL-6, IL-10 and H-propranolol. Following eutanasia, the intestinal villi were harvested for Western immunoblotting of P-glycoprotein.

RESULTS: There was no significant difference in the intestinal wall membrane permeability of propranolol between the burn and sham groups (2.05 ± 1.39 x 10^-9 vs 1.75 ± 1.02 x 10^-9 cm/sec). Burned rats had significantly lower TNF-α and IL-6 concentrations at the beginning of steady state, 60 minutes, as compared to sham animals (TNF-α: 6.15 ± 10.7 vs 59.9 ± 59.5; IL-6: 0.659 ± 19.39 vs 9.85 ± 12.5 pg/ml). TNF-α and IL-6 concentrations were also depressed at 80, 100 and 120 minutes. In contrast, IL-10 concentrations were not significantly different between the groups. No significant differences in the amounts of intestinal P-glycoprotein were detected.

CONCLUSIONS: Despite alterations in luminal TNF-α and IL-6 concentrations, the transcutaneous transport of propranolol is unaffected 24 hours following thermal injury in rats using the marker propranolol. Our results suggest that a major pathway for drug absorption is preserved following thermal injury. Moreover, the amount of the efflux protein, P-glycoprotein, appears preserved.

39. A review of albumin usage in the neurosurgical patient at the University of Kentucky Medical Center. Kimberly Varney, Pharm.D., Terry Cheak, B.S.N., Byron Young, M.D., Jimmi Hatton-Kolpek, Pharm.D., BCNSP; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: Controversy remains regarding the use of albumin in the neurosurgical (NS) population. Particular concern involves its use for prevention/treatment of subarachnoid hemorrhage (SAH)-induced vasospasm. Our purpose is to determine why and how much albumin we use in this population, thereby facilitating the establishment of guidelines.

METHODS: All neurosurgical patients receiving albumin between October 1, 1998 and May 31, 1999 were reviewed. A data form was utilized for collecting pertinent labs, pressures, fluids, doses, and attending physicians. In addition, a survey was mailed to members of the American Brain Injury Consortium (ABIC) in the U.S., Canada, and Europe. Included were questions regarding their patterns of albumin usage to which we could compare.

RESULTS: Overall, the neurosurgical service was found to be the second highest user of albumin in our hospital. Albumin was prescribed in 35 cases: vasospasm (49%), volume-expansion (40%), and organ preservation (11%). Approximately 1/3 of all SAH patients received albumin. One specific physician (out of five) used albumin in 65% of the SAH patients. Method of administration included continuous infusion (SAH), and bolus dosing. ABIC survey responses found similar inconsistencies in albumin use compared with ours.

CONCLUSIONS: Use in SAH patients constituted the majority of albumin prescribing, and their continuous infusion methods created high usage numbers. Our data demonstrated a lack of consensus and confirms the need for guidelines. The ABIC survey also indicated inconsistencies and the need for further study.
40. Empiric versus protocol-based neuromuscular blockade in critically ill patients. Robert M. McLaughlin, Pharm.D., Christian C. Toombs, B.S., Ph.D., Johanna M. Plamondon, B.Sc. (Pharm.), Graeme M. Rocker, M.A., D.M., FRCP, FRCP(C), Richard I. Hall, M.D., FRCP(C), FCCP; The Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: To compare empiric therapy (ET) to protocol-based therapy (PT) of neuromuscular blockade (NMB) in terms of cost, control of paralysis, and blood pressure variations.

METHODS: Thirty ET patients and 17 PT patients requiring NMB for at least six hours were prospectively studied for 8 months before and 4 months after an evidence-based NMB protocol was implemented as a medication order form in the medical/surgical/neurologic intensive care unit (ICU). The protocol promotes the use of pancuronium with vecuronium as an alternative if renal failure, hepatic failure, or hemodynamic failure is present. Comparisons between ET and PT included demographic data, hours of ICU stay, hours of NMB, hourly doses and acquisitions cost of neuromuscular blocking agents, fraction of hourly train of four measurements between one and three, and the occurrence of hypertension or hypotension within six hours of initiating NMB. Statistical analyses used the Student's t-test or Mann-Whitney U test for continuous data and chi squared test or Fisher's exact test for dichotomous data.

RESULTS: Demographic data, hours of ICU stay, and hours of NMB were similar between ET and PT groups. Protocol adherence was 88.2%. The mean hourly dose of pancuronium increased from 0.035 ± 0.13 mg during ET to 0.29 ± 0.37 mg during PT (p<0.005). The use of vecuronium was similar during ET and PT. Rocuronium and atracurium were not used after protocol implementation. The mean hourly acquisition cost of neuromuscular blocking agents decreased from $8.75 ± 7.08 CDN during ET to $5.11 ± 4.76 CDN during PT (p<0.005). Protocol use increased the fraction of train of four measurements between one and three from 32.5% to 52.3% (p<0.05) and reduced the occurrence of hypertension or hypotension from 36.7% to 23.5% (p<0.05).

CONCLUSIONS: Compliance with an evidence-based neuromuscular blocking protocol that promotes pancuronium use reduces drug costs, improves control of muscle blockade, and may reduce blood pressure variations associated with NMB.

41. Pharmacokinetics of intravenous levofloxacin in adult critically ill patients. Jill A. Rebeck, Pharm.D., Edward Abraham, M.D., Douglas N. Fish, Pharm.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: Critically ill patients may display alterations in the pharmacokinetics of many drugs. Levofloxacin disposition has not been studied in this population. Therefore, we evaluated the pharmacokinetics of intravenous levofloxacin in adult medical and surgical ICU patients.

METHODS: All subjects were studied for one dosing interval after estimated steady state was achieved. Blood samples were collected at predetermined intervals from arterial lines or intravenous lines following levofloxacin administration. Plasma levofloxacin concentrations were determined by validated HPLC assay. Data were analyzed using a noncompartmental pharmacokinetic model.

RESULTS: Eleven critically ill patients (7 male, 4 female; mean ± SD age: 57 ± 17 years, mean ± SD weight: 85 ± 24 kg, mean ± SD creatinine clearance: 69 ± 33 ml/min); mean ± SD APACHE II score: 21 ± 4. Eight patients received 500 mg, while 2 patients received 250 mg every 24 hours. The calculated (mean ± SD) t½, Clav, and Vd in all patients were 81 ± 25 hours, 147 ± 69 ml/min, and 1.3 ± 0.4 L/kg, respectively. In patients receiving 500 mg, calculated Cmax, Css, and AUC0-24 were 7.8 ± 1.0 mg/L, 1.1 ± 0.7 mg/L, and 21.3 ± 23.4 mg/hr/L, respectively. In patients receiving 250 mg, calculated Cmax, Css, and AUC0-24 were 3.2 ± 1.0 mg/L, 0.6 ± 0.5 mg/L, and 8.3 ± 8.5 mg/hr/L, respectively.

CONCLUSION: The results of our study are consistent with published values in other patient populations, indicating the pharmacokinetics of intravenous levofloxacin are not substantially altered in critically ill patients with normal or mildly impaired renal function.

Drug Delivery

44. The stability of total nutrient admixtures, Kwang Hyun Namgung, M.S., Suhkyun Lee, Pharm.D., M.S.; Sookmyung Women's University, Seoul, Korea.

PURPOSE: The objective is to study the stability of total nutrient admixtures (TNAs) containing lipid emulsions, amino acids and dextrose.

METHODS: The admixtures were prepared as 6 combinations in which 10% Intralipid® or Intralipose® were mixed with 3 different 10% amino acid solutions (Freeamine®, Intralasin® or Topanose®) in a glass bottle container. The mixing sequence involved transfer of amino acid solutions to the partial filled 1 liter glass bottle of 20% dextrose, followed by addition of fat emulsion. Electrolytes and heparin were added to the amino acid solution before compounding. The TNAs were tested initially and daily for 7 days at storage condition of 4°C in refrigerator or room temperature. Visual inspection was done first and measured for pH, osmolality, particle size of emulsion, paroxide value and the concentrations of amino acids, dextrose and fatty acids.

RESULTS: The apparent change of creaming has shown from 2 to 7 days according to the different TNA combinations and storage conditions. The measured parameters remained unchanged throughout the study except tryptophan.

CONCLUSIONS: The TNAs were stable at least 2 days at room temperature and 4 days in refrigerator. The TNAs can be stored for a limited period in refrigerator.

Education


PURPOSE: This study characterizes the types, frequencies and value of writing tasks found in clinical pharmacy practice. A secondary purpose was to explore any correlation between specific tasks and clinical practice types.

METHODS: A survey was developed, piloted and mailed to 129 clinical clerkship preceptors who practice in diverse settings representative of contemporary clinical pharmacy practitioners. The survey queried how often the practitioner wrote specific documents (e.g., formulary review), time on task and value to clinical practice for each document.

RESULTS: Sixty-six (51%) questionnaires were returned and sorted by clinical practice site. The majority of respondents were inpatient clinical practitioners (56%) or faculty/researchers (18%). Respondents reported writing 25 distinct documents in varying degrees of frequency. Respondents rated clinical reports and in-services as requiring the most time on task and also indicated they were the most valuable to their professional practices.

CONCLUSIONS: Because clinical pharmacy is a writing intensive profession, incorporation of specific didactic instruction into the pharmacy curriculum, based on the most frequent and important writing tasks, should be considered. In addition to pharmacy students, contemporary practitioners may benefit from continuing education instruction in professional writing. The results of this survey will assist the development of writing instruction curricula within the context of contemporary clinical pharmacy practices.

Endocrinology

48. The influence of cigarette smoking on Circadian rhythm of DHEA and DHEA-S, Patricia D. Kroboth, Ph.D., Maggie Folan, B.S.N., Roslyn A. Stone, Ph.D., Janet A. Amico, M.D.; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: During abstinence from smoking, withdrawal symptoms occur despite existing therapeutic strategies, including nicotine supplementation. To date, little attention has been focused on differences in Circadian secretion patterns of adrenal hormones between habitual smokers and never smokers and changes with acute smoking cessation. Smoking stimulates the release of arginine vasopressin, which increases ACTH and in turn, stimulates release of adrenal hormones. Epidemiological data indicate that relative to nonsmokers, habitual smokers have higher concentrations of DHEA-S. This study was designed to characterize the Circadian rhythm of DHEA and DHEA-S in habitual smokers and nonsmokers.

METHODS AND RESULTS: Data from four men (two smokers) and two women (one smoker) show that relative to nonsmokers, smokers have a Circadian rhythm characteristic by spikes during the daytime hours. DHEA-S concentrations were 2-fold higher in male smokers than in nonsmokers. In a second component of the study (evening), when one young male smoker abstained from smoking for 3 hours, then smoked three cigarettes within 30 minutes, a greater than 2-fold increase in DHEA concentrations was observed. CONCLUSIONS: There are no previous reports of the influence of acute smoking on DHEA concentrations, nor of habitual smoking on Circadian pattern. These findings in a small number of subjects have potentially important implications for management of the rate of decline of DHEA and DHEA-S concentrations during smoking cessation. There are also mechanistic implications because of the blunted DHEA Circadian pattern in depression.
and the well-known association between smoking and depression. Continued and more intensive study in additional subjects is warranted.

49. An evidence-based medicine approach for assessing the appropriateness of thyroid hormone suppression in multinodular thyroid disease. Grace K. Kim, Pharm.D., Frank M. Pucino, Pharm.D., M.P.H., Nicholas Sarlis, M.D., Ph.D., Eugene Byrd, Pharm.D., Robert Wesley, Ph.D., Monica C. Skarulis, M.D., Lynnette Nieman, M.D., Gyorgy Csako, M.D.; Clinical Center, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; Auburn University.

PURPOSE: To evaluate the effectiveness of thyroid hormone suppression on multinodular thyroid disease with systematic review of the literature, survey of endocrinology practitioners, and analysis of patient data.

METHODS: Relevant articles were identified through manual and on-line (MEDLINE) computer searches (1930-1998). Data were extracted from controlled studies, and the likelihood of reduction in nodule size by thyroid hormone suppression therapy (benefit ratio), 95% confidence intervals (CI), and statistical significance were determined. Meta-analysis was used for assessing combined benefit ratios. Published opinions (editorials, reviews, book chapters) and survey results from 22 NIH endocrinology practitioners were also analyzed. An automated database of 969 NIH patients receiving levothyroxine therapy was used for retrospective analysis of therapeutic outcomes in 30 patients with multinodular thyroid disease. Hill's criteria were applied to further assess the causal association between thyroid suppression and nodule reduction.

RESULTS: The combined benefit ratios determined by the random effects model and Mantel-Haenszel approaches were 5.09 (CI 2.46-10.55, p<0.001) and 5.62 (CI 2.74-11.53, p<0.001), respectively. Most published opinions were favorable or accepted levothyroxine suppression therapy either optionally or as the preferred initial therapy. An initial trial of mild-to-definite thyroid suppression therapy (TSH ≤ 1.00 mU/L) was suggested by 22 NIH endocrinology practitioners. Furthermore, 79% (23/29) of patients with multinodular thyroid disease managed by 24 NIH endocrinology practitioners had laboratory evidence of mild to moderate thyroid suppression (TSH ≤ 1.00 mU/L). Evaluation by Hill's criteria suggested a "possible-to-probable" causal association between thyroid suppression and nodule reduction.

CONCLUSIONS: Thyroid hormone suppression therapy increases the likelihood of nodule reduction in multinodular thyroid disease.


PURPOSE: This study compared diabetes knowledge in type-2 patients managed in general and specialized ambulatory settings. The objectives were to examine how patient demographics, previous diabetes education and treatment settings, relate to diabetes knowledge and to examine the correlation between diabetes knowledge and glycemic control.

METHODS: A written multiple-choice questionnaire was developed and pilot-tested to assess patients’ perceived and actual diabetes knowledge regarding medication, diet and general diabetes management. Questions were randomly distributed during office visits or by mail at a general medicine and endocrinology clinic. HgA1C values were gathered via chart review. Diabetes knowledge was quantified by perceived and actual knowledge separately.

RESULTS: Eighty questionnaires were included in the analysis (36 general, 44 specialized). There were no significant differences in patient demographics between sites. Endocrine clinic patients attended more diabetes education classes (p=0.014) and received more education (p=0.014) than general medicine patients. Total perceived knowledge scores were higher at the endocrine site (p=0.003). However, mean HgA1C and actual knowledge scores were not significantly different between sites. Linear regression revealed a significant correlation between perceived and actual knowledge for patients at the general medicine site (r²=0.51, p=0.001). No correlation was found between knowledge scores and HgA1C values at either site.

CONCLUSIONS: Similar patient populations treated at general and specialized ambulatory practices demonstrated comparable actual diabetes knowledge and glycemic control. Greater previous diabetes education appears to increase perception of knowledge. However, perception may not correlate with actual diabetes knowledge. Glycemic control does not correlate with perceived or actual diabetes knowledge.

51. Clinical outcomes of a multidisciplinary diabetes education and management program at a Veterans Administration Outpatient Clinic. Mary G. Amato, Pharm.D., M.P.H., Dora Santiago, M.S.N., Anita Moore, M.D.; University of Texas at San Antonio, San Antonio, TX.

PURPOSE: To assess effects of a diabetes education and management program on glycemic control and hyperlipidemia in type-2 diabetics with elevated HgA1C level.

METHODS: Expansion of an existing diabetes education program to include ongoing monitoring and optimization of treatment regimens was initiated in August 1998. The impact of this program in patients with HgA1C values over 9% was evaluated by comparing glycemic and lipid control in patients enrolled in this program (DMP) with those followed by a primary care provider (PCO). Patients with at least two HgA1C values and two primary care visits between April 1998 and March 1999 were included.

RESULTS: Of approximately 1700 diabetics at the clinic, 180 had HgA1C values over 9%, and 86 of these patients were in the DMP group. Eighty-two percent of patients had over a 2% drop in HgA1C versus 12% in the PCO group. Forty-seven percent of the DMP patients had over a 2% drop in HgA1C versus 12% in the PCO group. Eighty-two percent of patients in the DMP had low density lipoprotein values under 130 (1998 goal) versus 57% in the PCO group. No difference in triglyceride levels was seen.

CONCLUSIONS: The DMP has demonstrated improved glycemic control.

52. Diabeticogenesis and ketoacidosis with atypical antipsychotics. Daniel R. Wilson, M.D., Leo D’Souza, M.D., Nibar Sarkar, M.D.; The Lewis Center, Cincinnati, OH.

PURPOSE: With the advent of novel antipsychotic compounds that are relatively free of extrapyramidal symptoms, clinicians have shown increased interest in side effects that have previously not been the focus of attention. Recent case reports have suggested that some atypical antipsychotics may induce clinically significant alterations in glucose metabolism. The authors evaluated the risk of diabeticogenesis in a large state hospital cohort.

METHODS: The computerized records of all adults aged 18 and older in an academically affiliated state hospital were retrospectively reviewed over a 48-month period (May 1995 to May 1999). Patients treated with novel antipsychotics were identified as were persons evaluated for diabetes management. The rosters were collated and full charts of patients on both lists were reviewed with respect to age, sex, psychiatric diagnosis, drug treatment history, diabetic risk factors, and clinical association between glucose intolerance and treatment with atypical antipsychotics.

RESULTS: Results of preliminary data analysis revealed acute and marked glucose intolerance in 11 patients. Changes were not related to significant weight gain and typically occurred in the first 6 weeks. Six patients were treated with insulin at least transiently and four experienced diabetic ketoacidosis with referral to a tertiary care facility for intensive and life-saving medical care.

CONCLUSION: It is of considerable concern that at least some antipsychotics may be dangerously diabetogenic. A more extensive analysis of the larger statewide Ohio Department of Mental Health database is now underway to ascertain whether 1) all or specific medications are diabetogenic, 2) more assertive treatment monitoring is warranted, and 3) atypical antipsychotics are contraindicated in patients at high risk for new-onset diabetes.

53. Drug utilization review of acarbose in the Saint Louis Veterans Affairs medical center. Carrie F. Lee, Pharm.D., Carla Zellemann, Pharm.D., BCPS; St. Louis Veterans Affairs Medical Center; St. Louis College of Pharmacy, St. Louis, MO.

PURPOSE: Determine the effectiveness of acarbose in lowering HgA1C in the veteran population at the St. Louis Veterans Affairs Medical Center (VAMC). METhODS: A list of all outpatients currently receiving acarbose at the St. Louis VAMC was obtained from the electronic pharmacy files. Data on current diabetic agents received and HgA1C prior to and after addition of acarbose was gathered. Patients were excluded if HgA1C data was unavailable up to one year prior or six months after addition of acarbose. Statistical values were determined using the SigmaStat™ program.

RESULTS: One hundred forty-nine veterans were included and evaluated. The change in HgA1C was non-significant with the exception of the sub-group of veterans on a sulfonylurea and/or metformin with a HgA1C > 8 prior to acarbose addition. HgA1C was reduced by 0.6% (NS) in patients taking either a sulfonylurea or metformin prior to acarbose addition. Between group differences were non-significant with the exception of HgA1C reduction being greater in patients receiving oral therapy prior to acarbose than in those receiving two oral therapies prior to acarbose.

CONCLUSIONS: Acarbose had little effect on HgA1C overall. In this population, acarbose may be useful as an adjunct in patients on oral therapy who have not achieved adequate HgA1C reduction. Though not statistically significant, the reduction in HgA1C noted in patients on oral therapy prior to acarbose may be clinically significant. Thus, acarbose may be an adequate adjunctive agent in this patient population.


PURPOSE: The objective of this study was to determine if flutamide and testolactone decrease the total body clearance of cortisol in children with
congenital adrenal hyperplasia (CAH).

METHODS: Cortisol clearance studies were performed twice in eight children with CAH. The first study was conducted at the time of admission in patients who had received flumetamide and testosterone for at least three months. The second study was performed after a washout period of at least 48 hours. All patients received a continuous infusion of hydrocortisone (0.6 mg/kg/h) from 7:00 a.m. to 1:00 a.m. Blood samples for cortisol determination were collected hourly from 6:00 p.m. (baseline) to 3:00 a.m. Serum cortisol concentrations were determined using a fluorosence polarization immunoassay. Total body clearance (CLTb) was calculated using the equation CLTb = R0/Css (where R0 is the hydrocortisone infusion rate and Css is the steady state cortisol concentration).

RESULTS: The mean total body clearance of cortisol during treatment with flumetamide and testosterone was 154 ± 76 ml/min. Cortisol clearance after the medication washout period increased to 353 ± 186 ml/min. The difference in cortisol clearance was significant (p=0.0117, Wilcoxon signed rank test).

CONCLUSION: The combination of flumetamide and testosterone substantially decreases the total body clearance of cortisol in children with CAH. The mechanism and clinical significance of this effect have yet to be elucidated.

55. Glycemic control in medical inpatients receiving sliding scale insulin regimens versus routine antidiabetic medications: a pilot study. Lori M. Dickerson, Pharm.D., BCPS, Jonathon L. Sack, M.D., William J. Hueston, M.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Patients with diabetes are traditionally converted from their routine antidiabetic medication to a sliding scale insulin (SSI) during hospitalization. However, the benefits of SSI regimens versus routine medications are unclear. The purpose of this trial was to compare routine antidiabetic medications alone versus the combination of SSI and routine antidiabetic medications on the frequency/severity of glycemic excursions and length of stay in diabetic patients hospitalized for other comorbid conditions.

METHODS: Patients with diabetes hospitalized for other co-morbid conditions but not meeting criteria for hyperosmolar nonketotic coma, diabetic ketoacidosis, hyperglycemia (> 400 mg/dl) or hypoglycemia (< 50 mg/dl) were enrolled and randomized to receive either their routine antidiabetic medications alone or the combination of SSI and routine antidiabetic medications. Finger stick blood glucose (FSBG) are measured four times daily, and management of all medical conditions is instituted as part of usual care.

RESULTS: Comparisons of the groups randomized to SSI alone or the combination with SSI show no differences in age, gender, admitting diagnosis or average initial glucose on admission. Length of stay (days) for the two groups did not differ (3.67 versus 4.25, p=0.58). One episode of hyperglycemia occurred in the routine antidiabetic medication group and one episode of hypoglycemia occurred in the combination SSI group.

CONCLUSION: Preliminary results indicate that glycemic excursions occur in both groups but length of stay does not differ with the addition of SSI to routine antidiabetic medications in this population. Patient enrollment continues and additional results will be presented.

Gastroenterology

56. Clinical and economic outcomes of treating Helicobacter pylori in patients taking chronic acid suppression therapy. Patrick M. Klem, Pharm.D., Julie Himstreet, Pharm.D., Katie Bohnert, Pharm.D., Barry Carter, Pharm.D., Joel Levine, M.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: To compare symptoms, medical costs and quality of life in primary care patients with ulcer-like dyspepsia who are tested and treated for H. pylori with a control group treated with chronic antisecretory therapy alone.

METHODS: Historical controls (n=100) were identified by a pharmacy database and chart review of patients with documented or suspected PUD or ulcer-like dyspepsia taking chronic antisecretory therapy. Study patients were identified by a pharmacy database and treated by clinical pharmacists via a protocol developed with a gastroenterologist. Patients taking chronic antisecretory therapy for >3 consecutive months were recruited. Patients with predominant symptoms of GERD or chronic NSAID use were excluded. Patients who tested positive by serology were treated with lansoprazole, predominate symptoms of GERD or chronic NSAID use were excluded. Study patients were randomized to receive either their routine antidiabetic medications alone or the combination of SSI and routine antidiabetic medications. Finger stick blood glucose (FSBG) are measured four times daily, and management of all medical conditions is instituted as part of usual care.

RESULTS: Comparisons of the groups randomized to SSI alone or the combination with SSI show no differences in age, gender, admitting diagnosis or average initial glucose on admission. Length of stay (days) for the two groups did not differ (3.67 versus 4.25, p=0.58). One episode of hyperglycemia occurred in the routine antidiabetic medication group and one episode of hypoglycemia occurred in the combination SSI group.

CONCLUSION: Preliminary results indicate that glycemic excursions occur in both groups but length of stay does not differ with the addition of SSI to routine antidiabetic medications in this population. Patient enrollment continues and additional results will be presented.

58E. Rabeprazole: safety profile of a new proton pump inhibitor. David A. Johnson, M.D., Dennis Riff, M.D., Carlos Perdomo, Ph.D., John Jaskir, Ed.D., Dickerson, Peter S. Loewen, Pharm.D., Joel Barth, M.D.; Eastern Virginia Medical School, Norfolk, VA; Associated Gastroenterology Medical Group, Anaheim, CA; Eisai Inc., Teenek, NJ; Covance Inc., Princeton, NJ.

PURPOSE: Rabeprazole shows considerable promise across a range of indications – healing and healing maintenance of erosive or ulcerative gastroesophageal reflux disease (GERD), and healing of functional and gastric ulcers – provided that its clinical efficacy is supported by a favorable safety profile.

METHODS: To determine the safety profile of rabeprazole, an integrated summary was compiled using safety data from 3,536 subjects in 63 international clinical trials receiving rabeprazole for up to 1 year.

RESULTS: In short- and long-term controlled international studies, adverse events (AE) probably related to treatment, in at least 1% of treated patients, were headache (2.4% vs 1.6%), abdominal pain (2.4% vs 1.6%) and diarrhea (2.4% vs 1.6%) for rabeprazole and placebo, respectively. Rabeprazole 20 mg daily conferred no additional risk compared to the 10 mg dose for all indications. Hematologic parameters, liver and kidney function, cardiac enzymes, systolic/diastolic blood pressure, and ECG measurements showed no apparent dose-related effects. None of the AE suggested that rabeprazole affected any H K-ATPase other than the gastric proton pump. Rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin, theophylline, or phenytoin, although, like with all acid suppressants, individual patients may need monitoring and dosage adjustment when taking concomitant medications.

CONCLUSIONS: This analysis represents one of the most comprehensive and extensive sets of clinical data for a new proton pump inhibitor to date. The findings of this study confirm that rabeprazole is safe and effective and constitute the most detailed evaluation of this new compound to date.
60. Rabeprazole consistently effective for acid-related diseases based on worldwide studies. Karna Dev Bardhan, M.D., Norman Gitlin, M.D., Qinying Zhao, Ph.D., Yi-Lin Chiu, Nancy L. Lukasik, Barth, M.D.

**PURPOSE:** Rabeprazole, a new proton pump inhibitor, has been undergoing clinical investigation for gastroesophageal reflux disease (GERD) healing, long-term GERD healing maintenance, and healing of duodenal and gastric ulcers. To evaluate the efficacy of rabeprazole 20 mg for these indications, we compiled a summary of results from worldwide clinical trials.

**METHODS:** Results of placebo-controlled trials comparing rabeprazole 20 mg once-daily to omeprazole 20 mg or ranitidine 150 mg BID or QID for endoscopically determined GERD healing (≤ 8 wk), GERD maintenance (≤ 1 year), duodenal ulcer healing (≤ 4 wk), and gastric ulcer healing (≤ 6 wk) were compiled and summarized.

**RESULTS:** Efficacy data for 3 adequately controlled trials for each indication are presented. GERD healing rates for rabeprazole were 88% vs 15% for placebo (N=114, p<0.001), 92% vs 71% for ranitidine (N=316; p<0.001), and 95% vs 96% for omeprazole (N=197). GERD maintenance rates for rabeprazole were 88% vs 21% for placebo (N=222; p<0.001), 84% vs 22% for ranitidine (N=169; p<0.001), and 96% vs 94% for omeprazole (N=141). Duodenal ulcer healing rates for rabeprazole were 87% vs 45% for placebo (N=60; p<0.001), 88% vs 76% for ranitidine (N=335; p<0.005), and 99% vs 96% for omeprazole (N=201). Gastric ulcer healing rates for rabeprazole were 93% vs 55% for placebo (N=62; p=0.003), 89% vs 83% for ranitidine (N=335), and 93% vs 93% for omeprazole (N=233).

**CONCLUSION:** Rabeprazole is consistently effective for each indication based on integrated results of worldwide clinical trials.

Published in Gastroenterol 1999;116:A292-3.


**PURPOSE:** To compare lansoprazole (LAN) vs ranitidine (RAN) for symptomatic heartburn (HB) in a primary care setting.

**METHODS:** A total of 593 HB patients were randomized to one of 4 regimens: LAN 30 mg OD X 20 weeks (LAN/LAN), RAN 150 mg BID X 20 weeks (RAN/RAN), LAN 30 mg OD X 8 weeks, then RAN 150 mg BID X 12 weeks (LAN/RAN), or RAN 150 mg OD X 8 weeks, then LAN 30 mg OD X 12 weeks (RAN/LAN). The primary efficacy variable was HB assessment by patient diary.

**RESULTS:** ITT analyses compared second period HB diary data for step up (RAN/RAN vs LAN/RAN) or step down (LAN/LAN vs LAN/RAN). Patients stepped up to LAN experienced significantly less HB while patients stepped down to RAN experienced significantly more HB. Crossover patients (LAN/RAN and RAN/LAN) had less severe HB on LAN. LAN/LAN patients experienced significantly less HB than RAN/RAN patients throughout the entire 20-week study.

**CONCLUSION:** Neither step up nor step down strategies for heartburn in primary care appears optimal. Initiation and maintenance therapy with lansoprazole was superior to either a step up or step down approach.

Published in Gastroenterol, April 1999;116:A190.


**PURPOSE:** Peptic ulcer disease has been involved with Helicobacter pylori infection and antibiotic regimens are primary treatments. An optimal therapeutic regimen for eradication of H. pylori remains to be established. The objectives of this study were to evaluate the efficacy of omeprazole-based antibiotic regimens in bacterial eradication, healing of peptic ulcer and to identify factors affecting the efficacy.

**METHODS:** Seventy-seven patients were enrolled in the prospective, open-label trial from November 1999 to September 1998. H. pylori infection was identified with endoscopy, H. pylori stool and rapid urease test. The first group (OAC7) received omeprazole 20 mg twice daily for 4 weeks which was then continued for all, amoxicillin and clarithromycin for 250 mg twice daily for 1 week; the second group (OAC14), for 2 weeks on the same regimen as the first; and the last group (OACD) has taken bismuth in addition to the OAC7 regimen for 1 week. Eradication of H. pylori and healing of peptic ulcer were evaluated with endoscopy and tests for H. pylori before and after the end of the treatments.

**RESULTS:** There were no significant differences in eradication rates: 61% in OAC7, 55% in OAC14, 65% in OACD (p=0.817) and healing rates: 64% in OAC7, 65% in OAC14, 77% in OACD (p=0.193). Compliance affected eradication rates significantly among regimens (p=0.049). Twenty three cases (29%) complained of the minor side effects.

**CONCLUSIONS:** OAC7 was better in compliance of dosing schedule and showed less side effects with shorter duration and lower cost although there was no significant difference in efficacy.

63. The effect of multiple doses of fluoxetine on the pharmacokinetics and cardiovascular safety of cisapride in healthy volunteers. Qiying Zhao, Ph.D., Helen Pentikis, Ph.D., Ming Zheng, Ph.D., Mary Ann Wojcik, M.S., Peter Lee, Ph.D., Jean-Loup Parier, M.D., Ph.D., Luana Pesco-Koplowitz, M.D., Ph.D.; Janssen Research Foundation, Titusville, NJ; GloboMax LLC, Hanover, MD.

**PURPOSE:** To evaluate the effect of steady-state fluoxetine on the pharmacokinetics and cardiovascular safety of cisapride at steady state in healthy volunteers.

**METHODS:** Twelve male subjects were treated according to the following sequence: baseline (day 0); phase I (days 1-6), cisapride 10 mg QID; washout (days 7-13); phase II (days 14-44), fluoxetine 20 mg QD; and phase III, cisapride 10 mg QID (days 45-51) plus fluoxetine 20 mg QD (days 45-52). Blood samples for determining cisapride levels were collected at the end of phases I and III (days 6 and 5). Twelve-lead ECG recordings were obtained at baseline (day 0, baseline for phase I), washout (day 13, baseline for phases I and III), and the end of phases I and III (days 6 and 5).

**RESULTS:** Cisapride plasma levels reached steady state by day 5 during phases I and III. Geometric means of cisapride AUC0–24, Cmax, and Cmin for phase III were significantly lower than those for phase I. Fluoxetine had no effect on the Tmax or terminal t1/2 of cisapride. Changes from baseline in QTc, QT max and QTcl, avg were similar for the three treatments. No correlation was observed between changes from baseline in QTc, QTc, avg and QTc, clmax were similar for the three treatments. No correlation was observed between changes from baseline in QTc, QTc, avg and QTc, clmax were similar for the three treatments. No correlation was observed between changes from baseline in QTc, QTc, avg and QTc, clmax were similar for the three treatments. No correlation was observed between changes from baseline in QTc, QTc, avg and QTc, clmax were similar for the three treatments.

**CONCLUSIONS:** Fluoxetine does not inhibit cisapride metabolism. Cisapride 10 mg QID with fluoxetine 20 mg QD is well tolerated.

64. Pharmacokinetic/pharmacodynamic comparisons between Lansoprazole and pantoprazole in healthy subjects. Wei-Jian Pan, Ph.D., Yi-Lin Chiu, Ph.D., Roberta Keith, B.S.N., Betsy Pilmer, B.S.N.; Abbott Laboratories, Abbott Park, IL; TAP Holdings Inc., Deerfield, IL.

**PURPOSE:** To compare the pharmacokinetics/pharmacodynamics of 5-day lansoprazole 30 mg OD and pantoprazole 40 mg OD.

**METHODS:** Sixty-five healthy volunteers were randomized to 5-day lansoprazole 30 mg OD or pantoprazole 40 mg OD in a randomized two-way crossover experiment. Plasma samples were analyzed for days 1 and 5 and pharmacokinetic and pharmacodynamic evaluations were conducted at baseline and on days 1 and 5 of each period for pharmacodynamic evaluation.

**RESULTS:** Pharmacokinetic parameters, expressed as mean ± SD, and mean gastric pH were:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lansoprazole 30 mg OD</th>
<th>Pantoprazole 40 mg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>779.4 ± 2201</td>
<td>759.4 ± 2036</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>AUC0–24 (ng•h/ml)</td>
<td>1980 ± 1673</td>
<td>1948 ± 1753</td>
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<tr>
<td>Tmax (h)</td>
<td>3.35 ± 0.34</td>
<td>3.45 ± 0.27</td>
</tr>
<tr>
<td>Time Interval (h)</td>
<td>0.05 ± 0.38</td>
<td>1.05 ± 0.26</td>
</tr>
</tbody>
</table>

**CONCLUSION:** There were no significant differences in pharmacokinetic parameters between lansoprazole and pantoprazole. There was a trend towards higher gastric pH with pantoprazole compared to lansoprazole.
CONCLUSIONS: Pantoprazole 

Geriatrics

65. Vitamin K usage in the elderly compared to the American College of Chest Physicians' recommendations. Trang Y. Vo, Pharm.D., Mary Beth O'Connell, Pharm.D., BCPS; University of Minnesota; Institute for the Study of Geriatric Pharmacotherapy, Minneapolis, MN.

PURPOSE: To determine concordance between vitamin K use and the 1995 American College of Chest Physicians recommendations (ACCP) for hospitalized elderly patients.

METHODS: A secondary data analysis of a 23 center, retrospective chart review of 10,000 warfarin patients (version 7.0) were used to determine concordance.

RESULTS: In the high INR group, 55% of the 687 high INRs were treated in concordance; 61% for step 1, 7% step 2, 6% for step 3 and 19% for step 6. In step 1, 2, and 3, 54%, 5%, and 10% patients, respectively, had 75-100% of their high INR treated in concordance. Only 11% and 26% of patients with a minor or major bleed received vitamin K, respectively. Seven patients who did not have a high INR or a bleed received vitamin K, however, need for rapid reversal could not be assessed.

CONCLUSIONS: Majority of over-anticoagulated elderly patients was not treated in concordance with ACCP recommendations. More education and recommendation dissemination are required.

66. Nephrotoxicity risk assessment of aminoglycoside dosing in a geriatric VA population. Matthew T. Lane, Pharm.D., George A. Davis, Pharm.D.; Lexington VA Medical Center; University of Kentucky, Lexington, KY.

PURPOSE: Recent reports suggest that aminoglycoside nephrotoxicity in geriatrics is no greater than in younger populations. This study evaluated the overall incidence of nephrotoxicity occurring in geriatric patients receiving aminoglycosides in a VA medical center. The study also attempted to identify significant risk factors associated with aminoglycoside nephrotoxicity.

METHODS: All patients receiving gentamicin or tobramycin that were pharmacokinetically monitored during 1998 were identified. Those receiving aminoglycosides for less than 72 hours or baseline creatinine greater than 5 mg/dL were excluded. Data collected included age, baseline serum creatinine (Scr), maximum Scr within 1 week after therapy, significant medical diagnosis (diabetes, gout), use of concomitant nephrotoxic medications and intravenous contrast in the 30 days prior to therapy.

RESULTS: Nephrotoxicity was defined as a Scr elevation greater than 5 mg/dL. Sixty-eight received gentamicin or tobramycin during therapy. Eighty-eight received gentamicin. Dosing regimens of < 3 mg/kg/dose, 3-5 mg/kg/dose and 7 mg/kg/dose were utilized in 20, 13, and 48 patients, respectively. Nephrotoxicity occurred in 20 cases (25%), all receiving 7 mg/kg/day. Nephrotoxic medications, intravenous contrast and concurrent medical diagnosis were not found to be statistically significant risk factors.

CONCLUSIONS: Nephrotoxicity occurred more frequently in the patient population compared to historical values demonstrating risks of 5-7%. Eighty percent of patients were 65 years or older. Alternative antibiotics should be considered in this patient population whenever possible or more aggressive therapeutic drug monitoring may be warranted.

67E. Tolerance and efficacy of atypical antipsychotics in male geriatric inpatients. Swapan K. Verma, M.D., Claudia A. Orenge, M.D., Mark E. Kunik, M.D., Victor Molinari, Ph.D., Danielle Halle, M.S., Baylor, Houston, TX.

PURPOSE: The atypical antipsychotics are gradually becoming the mainstay of pharmacotherapy in the elderly. The present study examines the efficacy of risperidone and olanzapine treatment in 34 matched male patients admitted to a geriatric inpatient unit.

METHODS: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia, the Global Assessment Rating Scale (GARS) and the Geriatric Rating Scale for Side-Effects, the Extrapyramidal Rating Scale, and the Mini-Mental State Examination were administered at admission and discharge. Data were analyzed using t-tests to compare the differences between mean scores on these measures between risperidone and olanzapine groups.

RESULTS: Most of the patients on risperidone or olanzapine improved significantly with regard to less agitation, reduced positive symptoms, and higher global assessment of functioning. No significant differences were detected between the two groups with regard to length of hospitalization or reduction in scores on the PANSS and GARS. Both medications were equally well tolerated.

CONCLUSIONS: Both risperidone and olanzapine appear to be well tolerated and equally efficacious in the treatment of late-life psychoses and behavioral disturbances in elderly patients with dementia.


Health Services Research

68E. Creation of a tool to assess quality of pharmaceutical care documentation. Jay D. Currie, Pharm.D., Julie Kuhle, B.S., William R. Doucette, Ph.D., Jenelle L. Sobotka, Pharm.D., William A. Miller, M.S., Pharm.D., Randall P. McDonough, M.S., Angela L. Tice, Pharm.D.; University of Iowa, Iowa City, IA; The Iowa Pharmacy Association; Drake University, Des Moines, IA.

PURPOSE: This project was designed to develop guidelines as to the necessary data elements to be included in pharmacist documentation to allow the assessment of quality of pharmaceutical care delivered, and to develop a proposed process for assessing adherence to these guidelines.

METHODS: Consensus building took place in three steps. A review of the literature resulted in a list of 85 data elements to be considered in the documentation of care. A national practitioner panel reviewed the elements for applicability. Additional questions identified current documentation methods and strategies. A Delphi technique was then used with an expert panel of pharmacists and other health care providers to determine essential elements. This process was completed with three mailings, with final changes leading to consensus made at a group meeting.

RESULTS: The expert panel reached consensus on a listing of 27 essential elements. These encompassed both individual patient encounter and longitudinal patient record elements. A description of each data element was created and a quality assurance tool and method were developed to evaluate patient care plans. Implementation and guideline use recommendations were delineated.

CONCLUSIONS: This project resulted in guidelines as to the necessary data elements to be documented to allow assessment of the quality of pharmaceutical care provided. These guidelines, validated through consensus, can serve as the cornerstone of a quality assessment process to assure quality pharmaceutical care documentation and allow for assessment of the care provided. The tool developed should provide guidance both to pharmacists providing care and to quality assessment organizations reviewing pharmacist-provided care.


69. AAEP survey I: psychiatric emergency service structure and function. Glenn W. Currier, M.D., Michael H. Allen, M.D., Randolph J. Hilliard, M.D., Douglas Hughes, M.D.; University of Southern California, Los Angeles, CA; Denver Health, Denver, CO; University of Cincinnati, Cincinnati, OH; Boston VA Medical Center, Boston, MA.

PURPOSE: Although psychiatric emergency services (PES) are widely acknowledged as central to the modern mental health “system”, no consensus model for these services exists and there are few benchmarks, national standards or guidelines relevant to practice in this critical area. To address this problem, the American Association for Emergency Psychiatry (AAEP) conducted a comprehensive survey of PES characteristics during 1998.

METHODS: A 70-item questionnaire elicited data on a range of topics concerning the respondents’ settings and practice patterns. Participants were selected on the basis of membership in AAEP, the emergency psychiatry subspecialty organization, and administrative responsibility for a PES. More than 90% were in academic settings and the average tenure in a leadership position was 6.8 years. The response rate was 91% and included urban and rural settings around the country.

RESULTS: In this report, we present the highlights of provider and site characteristics including data on numbers of beds, visits, hospital admissions, locked capacity, local regulations, physical restraint, length of observation status treatment available in the PES, aftercare arrangements, mobile outreach, crisis respite, payer sources, recidivism, formal protocols, consultation to emergency medicine and medical “clearance” procedures. Respondents reported an average of 400 visits per month, a mean of 9.2 beds, and a mean length of stay of 9.0 hours. Medications are initiated in 82% and 51% provide their own aftercare for a mean of 2.6 visits.

CONCLUSIONS: The data suggest psychiatric emergency services are increasingly complex and organizationally unique.

Hematology

70. Standard nomogram for initial stabilization of warfarin dosage in patients with cerebrovascular diseases. Clarence Chant, Pharm.D., Mark J. Stack, PhD., Clarence Chant, Pharm.D.
PHARMACOTHERAPY Volume 19, Number 10, 1999

Gorman, M.D.; St. Michael's Hospital; University of Toronto, Toronto, ON, Canada; Wayne State University, Detroit, MI.

PURPOSE: This study was designed to evaluate the effectiveness, efficiency, and safety of a modified, institution-specific nomogram for initial dosing of warfarin for patients with cerebrovascular diseases as compared to traditional empiric dosing by physicians.

METHODS: Patients in the prospective group received daily warfarin doses in accordance with the nomogram and the measured international normalized ratio (INR). Patients identified retrospectively who had their warfarin dosage empirically determined by house officers served as the control group. Endpoints of effectiveness, efficiency, and safety of the nomogram, defined as the proportion of patients with therapeutic INR upon discharge, were required to achieve therapeutic INR, and major and minor bleeding episodes, respectively, were statistically compared using Chi square test and survival analysis.

RESULTS: Sixty and 34 patients were enrolled into the prospective and control groups, with a mean age 63 ± 16 and 65 ± 15 years, respectively. Primary indications for warfarin were thrombotic/embolic strokes or transient ischemic attacks. Patients in the prospective group achieved a therapeutic INR significantly earlier (p<0.02), resulting in a trend towards shorter length of stay (78.3 ± 30.9 vs 35.4 ± 36.4 days, p=0.06) when compared to the control group. Both groups had a similar proportion of patients achieving a therapeutic INR prior to discharge. A similar number of supra-therapeutic INR values occurred in both groups, as was the number of episodes of major or minor bleeding.

CONCLUSION: A modified, institution-specific nomogram for initial stabilization of warfarin dosages in patients with cerebrovascular diseases was more efficient and equally safe and effective as empiric dosing by physicians.


PURPOSE: The approval of a generic form of warfarin has generated debate over the appropriateness of therapeutic substitution with brand name warfarin. Minimal pharmacodynamic data is available to aid clinicians in this decision. The purpose of this project is to determine the current practice, views, and experience of anticoagulation clinics (ATCs) regarding generic warfarin substitution.

METHODS: A 39-item survey was designed consisting of check boxes, 5-point scales, and open ended questions. Surveys were sent to 570 ATCs in the United States registered with the Anticoagulation Forum. Survey questions examined product use, selection criteria, and factors influencing product preference.

RESULTS: The survey response rate was 177 (31%). Use of brand name warfarin was preferred by 118 (66.7%) clinics, generic warfarin by 8 (4.5%) clinics, and both brand and generic by 51 (28.8%) clinics. Many ATCs report concerns over potential differences in the response to or the safety of generic warfarin. Factors most often cited as important in the consideration of generic substitution include the possibility of life-threatening complications with suboptimal dosing and the efficacy to toxicity ratio of warfarin. Approximately one-half of ATCs report complications when switching to generic warfarin. The majority (77.7%) of anticoagulation clinics believe that current FDA bioequivalency guidelines are not adequate for warfarin. Approximately one-half of clinicians feel that third party payers mandate generic substitution.

CONCLUSION: Most ATCs prefer the brand preparation of warfarin over the generic due to lack of large, well-designed trials evaluating the pharmacodynamic response when alternating generic and brand warfarin.

72. Therapeutic range determination using the capillary and plasma activated partial thromboplastin time. Christopher R. Zimmerman, Pharm.D., Mark A. Touchette, Pharm.D., Suzan N. Kucukarslan, Ph.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: The objectives of this study were to establish therapeutic ranges for the capillary and plasma activated partial thromboplastin time (aPTT) and compare agreement in clinical decision making between methods.

METHODS: General medicine patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) receiving unfractionated heparin via a heparin nomogram were enrolled. Two consecutive paired blood samples were obtained. The CoaGucheck Plus™ (CCP) coagulometer and central laboratory were used to measure the capillary and plasma aPTT, respectively. A chromogenic factor Xa inhibition assay (therapeutic range: 0.3 - 0.7 U/ml) was used to determine a heparin level for all plasma samples. Therapeutic ranges for the laboratory and CCP were determined by regression analysis (y = 0.6211x + 0.0107, r² = 0.9799, x = heparin level).

RESULTS: Data from 104 samples (27 patients) were analyzed. Therapeutic ranges for the laboratory and CCP were similar at 62.7 - 105.5 seconds (r²=0.493, p<0.05) and 69.8 - 106.5 seconds (r²=0.417, p<0.05), respectively. Laboratory and CCP results agreed 71% of the time when compared against the heparin nomogram. When the laboratory and CCP derived aPTT values were interpreted using this nomogram (therapeutic aPTT = 55-85 seconds), a therapeutic heparin level was predicted in 8/23 and 10/23 samples, respectively. Sensitivity and specificity for the laboratory and CCP were 35% and 75% and 43% and 68% respectively.

CONCLUSIONS: The laboratory and CCP methods produced disparate aPTT results; however, similar clinical decisions in heparin adjustment occurred in each group. Heparin nomograms should be tailored to the instrument being used based on calibration of the aPTT against the heparin level.

Herbal Medicine

73. Vitamin supplementation and natural or herbal product utilization among ambulatory clinic patients at a university medical center. Melinda K. Lacy, Pharm.D., Shonee A. Metcalf, M.S., Patricia A. Howard, Pharm.D., Mark J. Webb, Pharm.D., James M. Backes, Pharm.D., oral. Kansas City, KS.

PURPOSE: The purpose of this study was to assess vitamin supplementation and natural or herbal product utilization among patients from various outpatient clinics at a university medical center.

METHODS: Data were collected prospectively over a six-month period. A front-and-back written survey was distributed to patients from several outpatient clinics (HIV, internal medicine, cardiology, lipid, warfarin, geriatric, and epilepsy) and the outpatient pharmacy. Surveys were completed either at home or at the clinic. Postage-paid envelopes were provided to facilitate response. Patients were asked to complete only one survey throughout the study period.

RESULTS: Of 634 surveys distributed to clinic patients, 315 were returned for a response rate of 50%. Forty-two more were completed at the outpatient pharmacy (no verified distribution count) for a final total of 357. Respondents were well matched for gender (52% female, 48% male), 46% were 60 years old, and 58% indicated current use of a vitamin/mineral and/or natural/herbal product. Most products listed by patients were vitamin/mineral supplements (69%, 352/511). Regarding natural/herbal therapy, 24% (87/357) of patients indicated current use of 57 products with gingin, ginkgo, and garlic most frequently noted. Most obtain information from physicians, magazines, or friends and the majority spend ≤$75/month. HIV patients account for the highest usage rate of natural/herbal products (50%, 13/26). Additionally, they spend ≥$75/month more frequently than any other group and are more likely to use the Internet for information.

CONCLUSION: These data show that the majority of ambulatory adults are currently taking a vitamin supplement and/or natural or herbal product.

74. Herb use in Anglo and Hispanic elders. Carla A. Zeilmann, Pharm.D., BCPS, Ernest J. Dole, Pharm.D., BCPS, Betty Skipper, Ph.D., Melvina McCabe, M.D., Tierona Low Dog, M.D., Robert Rhyne, M.D.; St. Louis College of Pharmacy, St. Louis, MO; University of New Mexico, Albuquerque, NM.

PURPOSE: The purpose of this study was to determine the types and prevalence of herbal medicines by elderly Hispanic and Anglo patients. Secondary objectives were to compare herb use by ethnicity, gender, age, socioeconomic status, and educational level, and to determine beliefs about herbal medicine.

METHODS: The study design was a cross-sectional, individually administered survey of patients at an urban medical center. To be included, patients needed to be at least 65 years of age, Hispanic or Anglo, an established patient in the clinic, not demented, and living independently.

RESULTS: One hundred eighty-six patients completed the study, 34 Hispanic males, 50 Hispanic females, 47 Anglo males, and 55 Anglo females. Forty-nine percent (n=91) admitted to using herbs in the previous year, most (75%) without telling their physician. The most common herbs were mint, chamomile, aloe vera, garlic, osha, lavender, and ginger. Patients most commonly used herbs for health care maintenance or self perceived problems such as gastrointestinal symptoms, skin conditions, cold symptoms, insomnia, and arthritis. Hispanic patients were more likely to obtain herb information from family, and Anglo patients were more likely to get information from the media. Although half of patients purchased herbs from a pharmacist, working, none received herb information from a pharmacist.

CONCLUSIONS: Herb users tend to be in the 65-74 year age range, female, have the lowest or highest level of education, and are in the lower end of the income scale. In general, Hispanic use more herbs than Anglos.

75. Survey of herbal therapies usage and patients' beliefs. Teresa S. Kleper, Pharm.D., William R. Doucette, Ph.D., Matthew R. Horton, Lucinda M. Buys, Pharm.D., Michael E. Ernst, Pharm.D., James D. Hoehns, Pharm.D., Hollie A. Kautzman, Pharm.D., Craig D. Logemann, Pharm.D., John M. Swegle, Pharm.D., Michael Ritho, Michael E. Kleper, Pharm.D.; University of Iowa; Iowa City, IA.

PURPOSE: 1) Describe demographics of patients using herbal therapies in Iowa; 2) assess patient willingness to discuss herbal use with health care providers; 3) identify commonly used herbal therapies; and 4) assess patient
beliefs regarding safety and efficacy of herbs. METHODS: A survey was distributed to two random samples: patients attending eight family care clinics and residents within the state (random mailing). Thirteen hundred surveys were distributed; 100 in each clinic and 500 mailings. Data were categorized according to respondent herb use and data from these groups were compared.

RESULTS: Seven hundred ninety-four surveys were completed (61%) with 42% of respondents reporting herbal use. Commonly used products were (descending order) aloe, garlic, ginseng, echinacea, and St. John’s wort. Herb users were predominately white females. Seventy-five percent of users regarded some form of vocational educational. Herb use was lowest among those reporting a high school degree as their highest level of education (p<0.05). Use of prescription medication was higher among herb users (p<0.05). Overall, users rated the safety and efficacy of herbs higher than non-users and believed their providers shared this opinion. Both groups believed that health care providers should be aware of herbal use and would provide this information.

CONCLUSIONS: Regardless of prevailing medical beliefs regarding herbal therapies, health care practitioners need to identify patients using these products in order to insure safety. This study demonstrates high herbal use in the state of Iowa and identifies patient populations most likely to use these products.

HIV/AIDS

76. A pharmacokinetic/pharmacodynamic model to characterize the CD4 response to recombinant interleukin-2 in HIV-infected patients. Stephen Piscitelli, Pharm.D., Alan Forrest, Pharm.D., Susan Vogel, B.S.N., Julia Metcalf, B.A., Michael Baseler, Ph.D., Joseph A. Kovacs, M.D.; National Institutes of Health, Bethesda, MD; SIAC, Frederick, MD; State University of New York at Buffalo, Buffalo, NY.

IL-2 is an immunomodulator that has been shown to increase CD4 counts in HIV-infected patients. PURPOSE: To develop a pharmacokinetic/pharmacodynamic model which simultaneously characterizes concentrations of IL-2, soluble IL-2 receptors (sIL-2r) and CD4 cells with IL-2 therapy. METHODS: Seven HIV-infected patients received 6-12 MU/d of recombinant IL-2 as a 5-day continuous intravenous infusion. Samples were collected daily for 10 days and at day 30 and analyzed for IL-2 and sIL-2r concentrations, and CD4 cells. The data were fit with IT2S to a model that included 24 compartments with formation driven by an indirect effect stimulatory model with a Hill-type function. CD4 was described by tissue and peripheral compartments with a direct effect to describe early trafficking and a stimulatory indirect effect to characterize delayed proliferation.

RESULTS: IL-2 concentrations peaked at 24 hours and declined by 70% during the remainder of the infusion. sIL-2r concentrations increased over 10-fold from baseline and peaked at day 5, returning to baseline by day 30. The mean CD4 count was 401 at baseline, initially decreased at 24 hours, then increased to a peak of 1740 cells/ml on day 6 before returning to a new baseline value of 497 at day 30. The model provided excellent fits of this complicated model with median r2 values of 0.96, 0.93, 0.96 for IL-2, sIL-2r, and CD4 respectively.

CONCLUSIONS: Increases in CD4 cells following IL-2 therapy can be characterized with a PK/PD model that incorporates IL-2 and sIL-2r concentrations and both direct and indirect effects. Such models may be useful to describe responses to subsequent regimens and interventions to enhance safety and efficacy.

77. Assessing AIDS knowledge and attitude between rural and urban Botswana women. Onalathia Johnson, Pharm.D., Craig A. Pedersen, Ph.D., Patty Fan-Harvard, Pharm.D.; Ohio State University, Columbus, OH.

Approximately 34% to 40% of all pregnant women are reported to be HIV-seropositive. The rising number of orphaned children is causing an enormous social burden in the country where more than 50% of households are motherless. Education is the mainstay of HIV/AIDS prevention. However, the effectiveness of these educational programs remains unknown.

PURPOSE: To assess and compare AIDS knowledge and attitude between rural and urban Botswana women using a published National Health Interview Survey AIDS questionnaire.

METHODS: Botswana women were surveyed in the city of Gaborone and from four villages, conveniently selected. The survey contained questions assessing general AIDS knowledge, HIV testing and self-perceived risk of becoming HIV infected.

RESULTS: A total of 321 (145 rural and 176 urban) Botswana women completed the survey. Higher annual income and levels of education were noted among urban than rural women (p<0.05). More rural women visited government facilities, traditional healers and religious healers while more urban women visited private doctors (p<0.05). A higher percentage of urban women demonstrated knowledge about AIDS as well as modes of HIV transmission. Only 35.7% of rural and 27.9% of urban women perceived the use of condoms as a very effective means of preventing the sexual transmission of HIV. Approximately 14% of rural and urban women self-assessed themselves at high risk of contracting HIV.

CONCLUSIONS: Mass media programs have been successful in educating the public about HIV/AIDS. However, there were a higher percentage of rural women who lacked understanding. More education is needed regarding condom use.


PURPOSE: To evaluate whether two separate MEMS® (Medication Event Monitoring System) Trackcaps™ are necessary to evaluate adherence to each of two antiretroviral medications, Combivir® (COM; lamivudine 150 mg, zidovudine 300 mg) and abacavir (ABC) given on the same BID schedule, in subjects from under-represented populations (UP).

METHODS: Two hundred antiretroviral-naive HIV positive adult subjects from UP (ethnic minorities, women, injection drug users) were enrolled in the H.E.A.R.T. and randomized (1:1) to receive routine counseling or an educational adherence intervention (T.I.E. Course) plus routine counseling. Subjects were required to have HIV-1 RNA > 40 and < 100,000 c/ml and CD4 lymphocytes > 50 cells/mm³. All subjects received COM 1 tablet BID plus ABC 400 mg BID for 100 days. Clearing with COM and ABC was assessed using MEMS® Trackcaps™ microelectronic monitoring devices to record the timing of each dose of study medication.

RESULTS: Preliminary MEMS® data are available for 73 subjects. Baseline demographics for these subjects are: median age 36, 74% male, 63% black and 26% Hispanic. Overall, 67% (40/59) and 64% (42/67) took 90-100% of COM and ABC doses, respectively. It was possible to match date of COM and ABC doses in 72 subjects. Considering all dose matches, the mean (SD) of the difference in time between doses was 1.6 (1.9) minutes. A range from 1 to 3 minutes was observed for differences in dosing times on a weekly basis.

CONCLUSION: Monitoring of either COM or ABC with MEMS® Trackcaps™ appears to provide a reliable estimate of adherence for both drugs.


PURPOSE: To characterize PK of dOTC, a novel nucleoside analogue, in healthy adult male volunteers.

METHODS: Study 1 was a randomized, cross-over, single-blind study in 15 volunteers. Each received 2 of 5 oral doses (100, 200, 400, 800, 1600 mg) of dOTC and placebo in three periods separated by 1 week. Sixteen plasma samples were collected over 24-48 hours with peak at day 5, returning to baseline by day 30. Median dOTC and placebo concentrations were determined using non-parametric methods. Statistical differences between arms were determined using parametric methods. Study 2 was a randomized, cross-over, open-label study in which 12 male volunteers with HIV infection received a single dose of dOTC (800 mg PO) while fed and fasted, separated by 1 week. Sixteen plasma samples over 72 hours were obtained, assayed (HPLC, CV < 8%), and PK parameters determined by S.H.A.M. methods. Statistical differences between arms were determined using non-parametric methods.

RESULTS: All doses were well tolerated. Study 1 demonstrated linear PK with low inter-subject variability. Median (CV %) plasma Cmax, CL/F, Vz, and Cz ranged from 9.7-19.2 (26.5-41.4) hr, 16.1-22.7 (15.8-29.6) L/hr/65 kg, 35.2-76.6 (21.6-57.0) L/65 kg, and 7.5-11.2 (19.2-39.4) mg/ml/800 mg, respectively. The goodness of fit was excellent, r² ranged from 0.995-1.0.

Study 2 demonstrated an absolute bioavailability of approximately 80% when IV and PO doses were compared. There were no significant differences in PK parameters following administration of a meal.

CONCLUSIONS: Single oral doses up to 1600 mg were well tolerated, dOTC is well absorbed and has a long plasma half-life. The PK appears to be linear with low intersubject variability and is not influenced by food. The elimination half-lives suggest dose intervals of 12-24 hours are reasonable. The PK appears to be linear with low intersubject variability and is not influenced by food.

80E. Use of rifabutin with protease inhibitors for HIV-infected tuberculosis patients. Jerry J. Stambaugh, Pharm.D., Masa Narita, M.D., E. Ibrahim, M.D., Jeanette Molyckeych, B.S.N., Elena S. Hollender, M.D., Arthur E. Pitchken, M.D., David Ashkin, M.D.; Memorial Hospital; University of Miami, Miami, FL.

BACKGROUND: Treatment of HIV-positive tuberculosis (TB) patients is complicated by reported drug-interactions between rifampicins and protease inhibitors (PIs). Few studies examine the use of rifabutin (RBT) with PIs.

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Infectious Diseases

81. Susceptibility of clinical coagulase positive and coagulase negative staphylococcus isolates to vancomycin over an eight-year period using ETEST methodology. Neil E. Klutman, Pharm.D., Michael Howard, B.A., Rebecca C. Horvat, Ph.D., Daniel R. Hintzorn, M.D., University of Kansas Medical Center, Kansas City, KS.

PURPOSE: Of great concern is the increasing antibiotic resistance including vancomycin resistance in gram-positive bacteria. We evaluated the susceptibility of Staphylococcus spp. cultured from patients over an eight-year period in order to 1) determine if an increase in minimum inhibitory concentration (MIC) for different species occurred; and 2) determine if an increase in MICs for coagulase positive (CP) or coagulase negative (CN) could be detected.

METHODS:  All gram-positive isolates (n=392) from patients with osteomyelitis from 1990 to 1997 were identified and speciated. The organisms were frozen at -70°C until testing. Susceptibility testing using ETEST methodology was performed. MICs of all S. aureus (methicillin sensitive or resistant), S. epidermidis (methicillin sensitive or resistant) and other coagulase negatives (S. haemolyticus, S. hominis, S. saprophyticus, S. warneri) were determined. Average (and range) MIC for each group over the eight-year period was calculated.

RESULTS: The average MIC (range in µg/ml) of S. aureus (n=295) was 1.6 (0.75-4). MRSA (n=66) was 1.52 (0.75-3), S. epidermidis (n=62) was 2.23 (1.5-4). MRSE (n=35) was 2.38 (1.5-4), all non-S. epidermidis CNs (n=95) was 2.4 µg/ml and all MRSEs (n=15) was 2.67 (1.8-4). Of concern was detection of 3 CPs isolates with a MIC of 4 µg/ml and 5 with a MIC of 3 µg/ml. In the CNS group, 26 isolates had a MIC of 3 µg/ml and 6 had a MIC of 4 µg/ml. In the CP group, regardless of sensitivity to methicillin had at least one isolate with a MIC of 4 µg/ml. The first isolate with a MIC of 4 µg/ml was from 1994.

CONCLUSION: No trend toward increasing average MIC to vancomycin was observed. The average MIC for coagulase negative isolates was higher. Concern regarding individual isolates with vancomycin MICs of 4 µg/ml is warranted and indicates the need to continue monitoring.

82. Comparison of serum and intracellular pharmacokinetics of azithromycin in healthy and diabetic subjects. Erika J. Earnst, Pharm.D., Michael E. Klepser, Pharm.D., Teresa B. Klepser, Pharm.D., Charles H. Nightingale, Ph.D., Lawrence G. Hunsicker, M.D., University of Iowa, Iowa City, IA; Hartford Hospital, Hartford, CT.

PURPOSE: The intracellular accumulation of the macrolide antibiotic azithromycin (AZTH) is an important characteristic for its effectiveness in treating intracellular pathogens. Other studies have shown that diabetic subjects display impaired leukocyte chemotaxis, phagocytosis and bacterial killing compared to non-diabetic individuals. Therefore, we compared the serum and intracellular (PMN) concentration of AZTH in healthy and diabetic individuals.

METHODS: Twenty-four subjects were given 500 mg of AZTH on day one following an overnight fast. Blood samples (85) were collected at 0, 1, 2, 2.5, 3, 6, 8, 12 and 24 hours following drug administration. Blood for measurement of the PMN concentration of AZTH was obtained before third dose and at 0, 1.5, 2, 2.5, 3, 6, 8, 12 and 16 hours after administration.

RESULTS: Mean (+ SD) pharmacokinetic parameters calculated using non-compartmental methods were determined.
PURPOSE: The new fluoronaphthyridone, trovafloxacin (IV/Po), has increased activity versus both methicillin sensitive and resistant Staphylococcus aureus. This agent may offer an alternative to intravenous vancomycin for the treatment of MRSA. This prompted us to evaluate the in vitro activity of trovafloxacin versus clinical blood isolates of both methicillin resistant and sensitive S. aureus (MRSA, MSSA). METHODS: Thirty-two clinical blood isolates (21 MRSA, 11 MSSA), were evaluated between December 1998 and May 1999. Minimum inhibitory concentrations were determined by the E-test method. NCCLS procedures were followed and susceptibilities were determined using NCCLS MIC breakpoints. RESULTS: The susceptibilities for 21 MRSA and 11 MSSA isolates to trovafloxacin were determined. 

<table>
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<th>Agent</th>
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<tr>
<td>Azithromycin</td>
<td>24 (67%)</td>
<td>0</td>
<td>12 (33%)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>23 (64%)</td>
<td>12 (33%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>36 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>36 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>36 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CONCLUSIONS: The activity of the newer FQs was excellent, even for the penicillin-resistant isolates. There has been an 18% increase in macrolide-resistant isolates over the past year. This resistance further decreases the utility of azithromycin as monotherapy for CAP. There has also been a 31% increase in penicillin resistant strains (23% low-level, 8% high-level). This increase is also reflected in decreased susceptibility to ceftriaxone. These data lead to the reevaluation of the standard of therapy for CAP at our institution increasing the role of the newer FQs.


PURPOSE: Differences between the newer quinolones are difficult to ascertain. A potential difference between the agents may be in the way the compound is acquired by, distributed within and cleared from human cells. We studied the pharmacokinetics and dynamics of 3H-grepafloxacin to determine these characteristics within human monocytes.

METHODS: Uptake and efflux of 3H-grepafloxacin into THP-1 human mononuclear cells was determined at 3 pHs and over 4 log antibiotic concentrations. Uptake studies were performed using cells stimulated with latex beads, lipopolysaccharide, zymogen A and in unstimulated cells. Energy dependence studies were conducted using verapamil and sodium azide. After 1 hour of monocyte loading with 3H-grepafloxacin, and samples collected at eight time periods. Subcellular organelles were isolated by ultracentrifugation. The antibiotic was distributed throughout the cytoplasm, nuclei, lysosomes, mitochondria and ribosomes in stimulated cells with the highest concentration in the cytosol.

RESULTS: Efflux followed first order clearance and was essentially complete within 110 minutes. Unstimulated monocytes were selected based on the possibility of another uptake process, such as passive diffusion. The efflux of 3H-grepafloxacin is partially blocked by the addition of verapamil, suggesting an energy dependent, calcium regulated process. Stimulated monocytes had an increased uptake of drug over time, with zymogen A providing the greatest increase in uptake over control.

CONCLUSION: Conclusions drawn from this work may provide insights into the mechanisms of development of quinolone resistance in gram-negative bacteria.


PURPOSE: To examine the effects of food on the pharmacokinetics of moxifloxacin following a single 400 mg dose.

METHODS: This was a randomized, blinded crossover study conducted in young healthy males. Moxifloxacin was given under two conditions separated by a one-week washout period: fasting and fed (immediately after a standardized high fat breakfast). Moxifloxacin serum concentrations were determined by a validated HPLC procedure with fluorescence. The pharmacokinetic parameters Cmax, Tmax, AUC(0-∞), AUC(0-t) and t1/2 were estimated using non-compartmental methods. Natural logarithms of AUC and Cmax were analyzed using ANOVA. Treatment effects were tested at the 5% significance level with two one-sided tests procedure and limits of 80% and 125% for AUC and 70% to 143% for Cmax.

RESULTS: Eighteen subjects were enrolled in the study; 16 were considered evaluable. The mean serum concentration profiles were similar between the two treatments. The geometric mean AUC(0-∞) values under fed and fasted conditions were almost identical, 37.7 vs 38.5 mg•h/L, respectively (90% CI of fed vs fasted was 95%-100%). Moxifloxacin absorption seems to be mildly delayed due to the effect of food with the median Tmax of 1.0 and 2.5 hours for fasted and fed conditions, respectively. Cmax values were 2.5 and 2.8 mg/L for the fed and fasted doses, respectively (90% CI of fed vs fasted was 0.78-0.98).

CONCLUSION: A single oral dose of 400 mg moxifloxacin was well tolerated when taken with and without food and was not associated with any clinically significant changes in Cmax or AUC0-∞ values.
90E. In vitro and in vivo influence of adjunct clarithromycin on the treatment of Pseudomonas aeruginosa. Khanh Q. Bui, Pharm.D., Mary A. Bangevicius, B.S., Charles H. Nightingale, Ph.D., Richard Quintiliani, M.D., David P. Nicolau, Pharm.D.; Hartford Hospital, Hartford, CT.

PURPOSE: Recent evidence has substantiated the benefits of macrolides against Pseudomonas aeruginosa (PSA). As adjunctive therapy, they may alter the course of infection through inhibition of biofilm formation or modulation of the host anti-inflammatory response. This study was undertaken to determine the adjunctive in vitro and in vivo effects of clarithromycin (CLR) with ceftazidime (CAZ) against a mucoid producing strain of PSA.

METHODS: A standard time-kill study was used for the in vitro experiment while a pneumonia model in neutropenic mice was used to observe the effects of different therapies in vivo. Mice were infected intranasally with 10^7 CFU of PSA and treated with oral CLR/subcutaneous CAZ monotherapy or with a combination of the two.

RESULTS: Following a 24-hour incubation with varying concentrations of CLR/CAZ monotherapy or in combination, synergy (≥2 log10 reduction) was noted with 0.5 x MIC CAZ combined with 0.5 or 2 x MIC CLR. In vivo, a statistical difference (p=0.04) resulted when mice were treated with CAZ x 2 plus CLR x 10 doses compared to mice receiving CAZ x 2 x 10 doses. No differences were observed when mice were treated with CAZ x 2 plus CLR x 10 doses as compared to CAZ x 2 x 10 doses (p=0.44) or with the combination containing a longer duration of CLR (p=0.19).

CONCLUSION: These data show that CLR has an adjunctive effect when administered with an antipseudomonal agent for the treatment of mucoid producing PSA in acute respiratory infection. The potential for use in humans will require additional studies.


91E. Pharmacokinetics and pharmacoeconomic evaluation of ticarcillin/clavulinate administered either as continuous or intermittent infusion with once-daily gentamicin. Khanh Q. Bui, Pharm.D., Paul G. Ambrose, Pharm.D., Edward M. Grant, Pharm.D., Charles H. Nightingale, Ph.D., David P. Nicolau, Pharm.D., Richard Quintiliani, M.D.; Hartford Hospital, Hartford, CT.

PURPOSE: Ticarcillin/clavulinate (T-C) is traditionally administered intermittently (II), but there is no reason why it cannot be given by continuous infusion (CI). In severe infections involving Pseudomonas aeruginosa, Enterococcus spp. or unusual Enterobacteriaceae, this agent is often combined with a once-daily dose of gentamicin (7 mg/kg) for synergy. Case reports and static in vitro studies have documented the potential for the inactivation of these two antibiotics when given concomitantly.

METHODS: This study was undertaken to determine the extent of an in vivo inactivation of ticarcillin (dosed as T-C), either as II (3.13 g IV q6h) or CI (500 mg/hr and 0.17 mg/hr of T-C, respectively), with and without gentamicin in healthy volunteers.

RESULTS: Eleven volunteers completed the II portion of the study with no statistically significant differences in serum levels of T-C or gentamicin in the AUC. CI dosages of T-C, equivalent to three T-C doses given in the presence of gentamicin. In the nine volunteers dosed with a CI of T-C, a statistically significant (p<0.008) reduction in ticarcillin (70 vs 55 µg/ml) was observed following the administration of gentamicin.

CONCLUSION: Although the inactivation of ticarcillin resulted in lowered concentrations during CI, this reduction should be of minimal, if any, relevance clinically since the concentrations exceed the MIC for organisms encountered with this drug. Assuming no difference in clinical outcomes where T-C is given by CI or II, the CI method becomes an attractive option owing to the major economic gains obtained.


92. Serum enhances the in vitro activity of fluconazole against Candida albicans. Erika J. Ernst, Pharm.D., Derek Adams, Michael E. Ernst, Pharm.D., Michael E. Klepser, Pharm.D.; University of Iowa, Iowa City, IA.

PURPOSE: The purpose of this study was to evaluate the effect of normal and heat-inactivated human serum on the minimum inhibitory concentration (MIC) of fluconazole against Candida albicans, and to compare the effect of serum from healthy patients versus diabetic patients’ serum.

METHODS: MICs were conducted according to the NCCLS guidelines (M-27P), and with the addition of 10% human serum. RPMI with MOPS was used for the culture medium. Six isolates of C. albicans were selected for study. These isolates have been studied previously, and MICs in the absence of serum range from 0.25 to >28 µg/ml. Serum was collected from four healthy and 11 diabetic patients who had not received any agent with known antifungal activity within one month. MICs were conducted in duplicate.

RESULTS: The addition of serum to the human serum, either normal or heat-inactivated, decreased the fluconazole MIC in 5 of 6 isolates tested. The MIC was similarly reduced by serum from healthy or diabetic subjects.

CONCLUSIONS: Fluconazole activity against less susceptible and resistant isolates of C. albicans is increased with the addition of serum in vitro, as seen by the decrease in MIC. This effect was not altered by heat inactivation of serum, and was consistent in healthy and diabetic subjects.

93E. Comparative bactericidal activities of ciprofloxacin, clinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, and trovafloxacin assessed in a dynamic in vitro model against Strepnotococcus pneumoniae. Michael E. Klepser, Pharm.D., C. Rosemarie Petzold, B.S., Paul Rhomberg, B.S., Gary V. Doen, Ph.D.; University of Iowa, Iowa City, IA.

PURPOSE: The goal of this study was to compare the bactericidal dynamics of six quinolones against S. pneumoniae.

METHODS: Using a dynamic in vitro model, we constructed time-kill profiles for ciprofloxacin (CIP), clinafloxacin (CLIN), grepafloxacin (GREP), levofloxacin (LEVO), moxifloxacin (MOXI), and trovafloxacin (TROV) against three isolates of quinolone-susceptible S. pneumoniae. Three pharmacokinetic profiles were evaluated for each of the study agents (600 µg AUC x 1, AUC x 10, and 10 x AUC). Target 24-hour AUCs were based upon human pharmacokinetic data resulting from maximal daily doses of each agent. All experiments were conducted over 48 hours and performed in duplicate. The rates and extent of reduction in CFU/ml were compared and presence of regrowth, if any, was noted.

RESULTS: Against all three isolates CIP was the least active agent. At regimens simulating the human 24 hour AUC, CIP resulted in an initial, modest decline in CFU/ml; however, by 48 hours the CFU/ml returned to or exceeded the starting inocula. At the AUC, LEVO resulted in mixed bacteriostatic and bactericidal activity among the isolates. The remaining agents yielded bactericidal (99.9% reduction) activity by 48 hours at the AUC. At 1/10 x AUC CIP and LEVO produced no inhibitory effect, GREP exhibited bacteriostatic activity, TROV mixed static and cidal activity, and CLIN and MOXI resulted in significant reductions in CFU/ml by 48 hours.

CONCLUSIONS: In this dynamic in vitro model of infection, the quinolones demonstrated varying degrees of activity against S. pneumoniae. The rank order of activity is CIP (least active) << LEVO < GREP < TROV < CLIN, MOXI (most active).


94E. In vivo tissue activity of high-dose liposomal amphotericin B in a neutropenic murine candidal thigh infection model. Russell E. Lewis, Pharm.D., Michael E. Klepser, Pharm.D., Stephen C. Piscitelli, Pharm.D., Andreas Groll, M.D., Veronika C. DeLallo, Pharm.D., Richard Quintiliani, M.D., Erika J. Ernst, Pharm.D., Thomas J. Walsh, M.D., Michael A. Pfaffer, M.D.; University of Iowa, Iowa City, IA; National Institutes of Health, Bethesda, MD; Hartford Hospital, Hartford, CT.

PURPOSE: To compare the in vivo fungicidal activity of amphotericin B (Amb-D) and high dose liposomal amphotericin B (L-Amb) using a neutropenic murine thigh infection model.

METHODS: Swiss-Webster mice (20-23 g) rendered neutropenic with cyclophosphamide pretreatment were injected with 100 mcl of a standardized Candida albicans (ATCC 90028) suspension to produce a localized thigh infection. Mice were then treated intravenously with six-fold escalating total daily dosages of either L-Amb (5 mg/kg-30 mg/kg/day) or Amb-D (0.5-2 mg/kg/day) dosed at q4, 8, 12, and 24 hour intervals. At predetermined timepoints following dosing (T = 0, 4, 8, 12, and 24 hours), mice were sacrificed, and thigh tissue was aseptically removed, homogenized, and plated on potato dextrose agar for colony count determination. Single dose pharmacokinetic studies of serum and thigh tissue concentrations were performed and analyzed by HPLC.

RESULTS: L-Amb dosed at 30 mg/kg q24h (tissue AUC24h of 60.16 µg/ml) was the most active of all regimens tested; achieving a 2-log10 decline in tissue fungal burden by 24 hours. Amb-D at 2 mg/kg/day reduced the fungal burden in the thigh by 0.5-log10. This tissue AUC24h for L-Amb averaged <10% of its parent serum AUC24h. Good correlation was noted between tissue AUC24h and reduction of tissue fungal burden by a sigmoid Emax model (r=0.975).
CONCLUSIONS: High-dose L-Amb is better tolerated and improves early antifungal efficacy over Amb-D in the murine thigh model. Dosage escalation with L-Amb is a viable strategy for improving antifungal efficacy where Amb-D penetration is initially poor.


95E. Reduction in the incidence of nosocomial vancomycin resistant enterococcus infections by implementation of an antimicrobial formulary control process. Vikas Gupta, Pharm.D., BCPS; Owen Healthcare Inc., Lombard, IL.

BACKGROUND: Studies have also shown that decreasing inappropriate use of vancomycin, third generation cephalosporins and clindamycin can significantly reduce the fecal colonization rates of vancomycin resistant enterococcus (VRE). Clin Infect Dis 1996;23:1020-5. The occurrence of nosocomial VRE infection and percentage of VRE isolates at our institution had increased from 8 cases in 1994 and 13% in 1995 to 14 cases and 18% in 1996, prior to implementation of a comprehensive antimicrobial formulary control process.

PURPOSE: To present results of a comprehensive approach which evaluated antimicrobial usage, susceptibility trends and nosocomial and community-acquired VRE infection rates at the hospital.

METHODS: The percentage of VRE, and the occurrence of nosocomial and community-acquired VRE infections were evaluated from 1994-1998. Antimicrobial usage was evaluated from 1996 to 1998 on a cost per adjusted patient day (APD) and g/1000 APD or g/100 patient days for third generation cephalosporins, vancomycin, and expanded spectrum aminoglycosides, piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanate (ZUTJ). A total of 70 patients were enrolled, 30 patients in each of the two study periods.

RESULTS: The occurrence of nosocomial VRE infection and percentage of VRE isolates decreased from 14 cases and 18% in 1996 to 8 cases and 15% in 1998. The occurrence of community-acquired VRE infections increased from 12 cases in 1994 to 29 cases in 1998. Antibiotic costs decreased from $13.89/1000 APD in 1996 to $10.89/1000 APD in 1998. Use of third generation cephalosporins, vancomycin and ZUTJ decreased from 230 g/1000 APD, 100 g/1000 APD and 115 g/100 APD in 1996 to 80 g/1000 APD, 60 g/1000 APD and 62 g/100 APD, respectively. Additionally, there were significant differences in the early and late periods, respectively. Although not significantly different, the percentage of oxacillin non-susceptible S. aureus (ORSA) isolates that were not susceptible to ciprofloxacin, clindamycin, erythromycin, and trimethoprim-sulfamethoxazole were 75.9%, 79.3%, 100%, and 65.5%, respectively (early) and 91.7%, 100%, 100%, and 66.7% (late). No changes in prevalence of E. faecium occurred however, more E. faecium were resistant to ampicillin and vancomycin in the late time period (p<0.05).

CONCLUSION: The predominant isolates have remained relatively constant during the time period evaluated. Reduced S. aureus susceptibility to oxacillin is reflected in other classes of antimicrobials. The high rate of ORSA in the community may warrant re-evaluation of empiric therapy in selected patients.


98. Molecular mechanisms of the immunomodulatory activity of amphotericin B in human monocytic cells. P. David Rogers, Pharm.D., M.S., Jonathan K. Stiles, Ph.D., John D. Cleary, Pharm.D., M.S.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: Amphotericin B (Amb) has been shown to exhibit immunomodulatory properties including cytokine activation, enhancement of macrophage activation, and inhibition of chemotactic responsiveness and activity of neutrophils. The purpose of this study was to identify differentially expressed genes encoding immunomodulatory proteins in response to Amb in human monocytic cells.

METHODS: Human monocytic cells (THP-1) at 10⁶ cells/ml were equilibrated for 24 hours at 37°C in 5% CO₂ in supplemented RPMI. Cells were then exposed to either Amb 5 µg/ml or media alone for 24 hours. The cell pellets were collected by centrifugation and total RNA was isolated using the guanidine isothiocyanate method. Reverse transcription of RNA from each isolate was performed using an oligo-dT primer. The resulting cDNAs were labeled with 3²P) dATP and used as probes. A complementary DNA gene array was used to compare mRNA populations from cells exposed to the two experimental conditions. The arrays were prehybridized for 30 minutes at 68°C and then hybridized with the probes at 68°C for 60 hours. The arrays were then washed and exposed to autoradiography. The two arrays were normalized for expression of housekeeping genes. Gene expression patterns were then compared for identification of differentially expressed genes.

RESULTS: Differential expression patterns were observed for several genes including those encoding immunomodulatory cytokines. The following data were obtained: C-type lectin domain containing 4 (CLEC4A), CC-chemokine receptor 5 (CCR5), monocyte chemotactic and activating factor (MCAF), and monocyte-derived neutrophil chemotactic factor (MDNCF).

CONCLUSION: Amb activates human monocytes to encode proteins that modulate immune function. This may explain the immunomodulatory properties observed with this agent.

infection (all p<0.05). The mean length of ICU stay was 25 days and 9 days for case and control patients, respectively (p=0.05). Sites of isolation included blood (21.4%), urine (75.9%), wounds (75.9%), respiratory (75.9%), CNS (14.3%), and other (14.3%). Twenty-three isolations (66%) represented colonization.

CONCLUSION: In the ICU setting at our institution, risk factors for colonization or infection with S. maltophilia are multifactorial.


PURPOSE: The purpose of this study was to identify differentially expressed genes in fluconazole resistant isolates of C. albicans that might contribute to fluconazole resistance.

METHODS: Differential display was used to compare mRNA levels from isogenic matched sets of clinical isolates obtained from two patients who developed candidiasis caused by fluconazole resistant strains of C. albicans while receiving therapy. Isolates were grown in brain heart infusion broth at 37°C in a shaking incubator until mid-log phase. The cell pellets were collected by centrifugation and RNA was isolated using the guanidinium isothiocyanate method. Reverse transcription of RNA from each isolate was performed using an 18 base primer for the first strand synthesis. Second strand synthesis and PCR amplification was completed using the same primer for a total of 40 cycles. The resulting products were analyzed on a 6% acrylamide gel and autoradiographed. Complementary DNA fragments corresponding to several apparently differentially expressed mRNAs were recovered and sequenced.

RESULTS: Several complementary DNA fragments observed to be differentially expressed in resistant isolates sequenced from putative open reading frames for the CDR99, POR1, GCN1, STA1, RPA190, verporlin and CEX1 genes in Candida albicans.

CONCLUSIONS: The putative gene products for these genes are involved in a multitude of cellular functions including efflux of intracellular toxins, mitochondrial transport of NADH, translational control, and RNA polymerase activity. Our results suggest that these genes may be involved in fluconazole resistance in this pathogenic fungus and may serve as potential pharmacologic targets.

101E. Efficacy and safety of ciprofloxacin oral suspension versus TMP/SMX for treatment of community- and nursing home-residing elderly women with acute urinary tract infection. I. Gomolin, M.D., P. Siani, M.D., D.A. Hawkerston, M.S., A. Heyd, Ph.D., Gurwin Jewish Geriatric Center, Commack, NY; Welborn Clinical Research, Evansville, IN; Bayer Corporation, West Haven, CT.

PURPOSE: To compare the efficacy and safety of ciprofloxacin oral suspension (CIP) compared to trimethoprim/sulfamethoxazole (TMP/SMX) oral suspension among elderly women with acute urinary tract infections (UTI).

METHODS: Prospective, open label multicenter study among elderly women (≥65 years) residing in the community or in a nursing home with an UTI. Patients were randomized to a 10-day oral suspension regimen of either CIP (250 mg [5 mL] Bid) or TMP/SMX (160/800 mg [20 mL] Bid). Clinical response at 4 to 10 days post-therapy (end of therapy) was the primary outcome measure.

RESULTS: Of 261 enrolled women, 86 patients in each treatment group had outcome measures.

response at 4 to 10 days post-therapy (end of therapy) was the primary outcome measure.

No single agent demonstrated bacteriologic activity. Gentamicin combined with flucloxacin or cefazidime demonstrated the best synergy activity. Combining either piperacillin or cefazidime with levofloxacin or sparfloxacin, as well as levofloxacin with gentamicin demonstrated some activity.

CONCLUSIONS: The newer fluoroquinolones have variable activity against AXX alone. β-lactam/gentamicin combinations appear to be most active against the isolates tested. Piperacillin or cefazidime combined with gentamicin were the most active combinations. Resistance was common with trovafloxacin and gentamicin in AXX isolates. AXX infections with AXX may be best treated with combination therapy including a β-lactam and gentamicin.

Presented at the 99th General Meeting of the American Society for Microbiology, Chicago, IL, May 30-June 3, 1999.

104E. Effect of antibiotics on human polymorphonuclear neutrophil apoptosis. Paul A. Silverman, Pharm.D., Daniel P. Realy, Pharm.D., Alice N. Nkedy, Ph.D., Ian Alan Holder, Ph.D., G. Babcock, Ph.D.; Shriners Hospitals for Children; University of Cincinnati, Cincinnati, OH.

PURPOSE: We and others have previously shown that antibiotics demonstrate differential effects on endotoxin release from gram negative bacteria with the subsequent production of inflammatory and antinflammatory cytokines. We have also demonstrated antibiotic-mediated upregulation of CD4 and CD11a, as a result of bacterial killing. Since these other factors have been linked to cellular apoptosis, the aim was to evaluate the direct and indirect effects of representative antibiotics, as a result of bacterial killing, on PMN apoptosis.

METHODS: EDTA-containing whole blood was collected from healthy subjects and incubated (37°C/4h) with and without K. pneumoniae (Kp 1.0 x 10⁶ CFU/ml) plus (in μg/ml) cefazidime (50; TAZ); gentamicin (5; GEN), ciprofloxacin (5; CIP), trovafloxacin (5, TRO), tetracycline (5; TET), doxycycline (5; DOXY), erythromycin (5; ERY), azithromycin (5; AZI), Kp LPS (10) or PMA (0.04). After staining with FITC-labeled annexin V and 7-aminoactinomycin D, RBCs were lysed, cells were read by flow cytometry and apoptosis was defined by staining.

RESULTS: In the absence of Kp infection, antibiotics increased apoptosis 56% (range 25-94%) on untreated cells (p<0.002). AZI, ERY, TRO and TET...
105E. Efficacy and safety of moxifloxacin versus clarithromycin for the treatment of community-acquired pneumonia. C. Fogarty, M.D., Lawrence Bonapace, Pharm.D., David Haverstock, M.D., Roger L. White, Pharm.D., Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: To evaluate the efficacy and safety of moxifloxacin vs clarithromycin in the treatment of community-acquired pneumonia (CAP).

METHODS: In a prospective, double-blind, multi-center clinical trial, 474 adult patients were enrolled with signs and symptoms of CAP. Patients were treated for 10 days with either oral moxifloxacin 400 mg once daily or clarithromycin 500 mg twice daily. Efficacy was assessed at the end-of-therapy (0-6 days post-therapy), follow-up (14-35 days post-therapy), and overall (end-of-therapy plus follow-up).

RESULTS: Among 473 intent-to-treat patients, 382 (81%) patients were included in the efficacy analysis. Fifty-six percent of patients had a pre-therapy causative organism identified (i.e., 277 organisms among 214 patients). The most common organisms identified included: Chlamydia pneumoniae (36%), Mycoplasma pneumoniae (16%), Haemophilus influenzae (14%), and Streptococcus pneumoniae (13%). The overall clinical resolution rates for the efficacy-valid population were 95% for both moxifloxacin and clarithromycin (95% CI = 93.7%, 96.3%). Bacteriologic success at follow-up, including end-of-therapy failures, was 96% for both treatment groups (95% CI = 95.8%, 96.6%). While drug-related events were equal in both moxifloxacin-treated patients (35%, 84/237) and clarithromycin-treated patients (34%, 81/236), only 6 (2%) moxifloxacin patients had study drug discontinuation because of an adverse event, as opposed to 12 (5%) clarithromycin patients. In both treatment groups, nausea and diarrhea were the most commonly reported adverse events (8%-%).

CONCLUSIONS: Moxifloxacin 400 mg once daily was as effective and as safe as clarithromycin 500 mg twice daily in the treatment of adult outpatients with CAP. Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

106E. Determination of antibiotic effect in an in vitro model: comparison with an established animal model. Charles R. Bonapace, Pharm.D., Lawrence V. Friedrich, Pharm.D., Roger L. White, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Animal infection models have historically been used to study pharmacodynamic (PD) relationships. Similar results/conclusions could theoretically be produced using an in vitro PD model as an alternative.

METHODS: We compared the antibiotic effect of ticarcillin, administered in various dosing regimens, against Pseudomonas aeruginosa ATCC 27853, under conditions analogous to that previously performed in a murine thigh infection model (Vogelman, et al. J Infect Dis 1988;158:831). Ticarcillin dosages of either 48, 96, 192, or 384 mg/day were administered at 1-, 2-, 4-, 8-, and 24-hour intervals into the central compartment of a 2-compartment model. Drug concentrations and colony counts were determined over 24 hours. Linear regression was used to assess the relationship between % T > MIC and number of CFU/ml from 0 to 24 hours for matched regimens in the in vitro and animal models based on % T > MIC.

RESULTS: % T > MIC was the PD parameter most associated with the log CFU/ml from 0 to 24 hours in the in vitro model. The % T > MIC log CFU/ml regression equations in the murine and in vitro models were similar and the % T > MIC log CFU/ml regression equations in the murine and in vitro models were similar and the % T > MIC log CFU/ml regression equations in the murine and in vitro models were similar and the % T > MIC log CFU/ml regression equations in the murine and in vitro models were similar. The % T > MIC log CFU/ml regression equations in the murine and in vitro models were similar. Further comparative studies of these models utilizing a variety of antimicrobials and organisms are warranted.


107E. Comparative activity of trovafloxacin and tobramycin, in combination with piperacillin and cefepime against clinical isolates of Acinetobacter baumannii assessed by three different methods. Charles R. Bonapace, Pharm.D., Roger L. White, Pharm.D., Lawrence V. Friedrich, Pharm.D., Linda B. Mihm, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Acinetobacter baumannii (AB) has become a problematic pathogen in many institutions due to development of multiple drug resistance; combination therapy may therefore be attractive or necessary.

METHODS: We performed synergy testing using time-kill (TK), checkerboard (CB), and epilseriplas test (ET) on 10 clinical isolates of AB with trovafloxacin (TV) and tobramycin (TM) in combination with cefepime (CF) and piperacillin (PI). Results from TK were based on duplicate 0- and 24-hour observations while microtiter plates for CB were read after 18 hours of incubation at 35°C. Concentrations of each agent in the TK combinations included 2 x MIC of TV plus 1/2 x MIC CF and 2 x MIC plus 1/2 x MIC CF. Standard definitions were used to define synergy (SI, additivity/indifference (A/I), and antagonism (A) for all methods. Ranges of MICs (µg/ml) of TV, TM, CF and PI were 0.03->

ACCP 1999 ANNUAL MEETING ABSTRACTS

Managed Care


PURPOSE: To compare the drug formularies of 11 managed care organizations (MCO) for compliance with minimum guidelines based on specific AHFS categories and overall clinical utility.

METHODS: Each MCO participating in TennCare submitted an electronic version of their 1997 drug formulary upon the request of the state TennCare Bureau. An integrated computerized database was created which included generic drug name, route of administration, prior authorization status, and

Clinical analysis of drug formularies for managed care organizations participating in TennCare.
AHFS category by MCO. Descriptive comparisons among formularies were performed on a computerized spreadsheet and served as indicators for the clinical utility of each formulary.

RESULTS: The formularies complied to the guidelines with levels that ranged from 91 to 99%. The average percentage of the number of drugs available per AHFS category for all MCOs was 59% (range = 49 to 93%). Of the 971 agents in a TennCare-specified AHFS category, 401 (41%) were included in all MCOs and 379 (39%) were included in the majority of the programs. The average percentage of drug categories requiring prior authorization for all MCOs ranged from 1% to 23% (average = 10%). Of the 349 agents available in the TennCare-specified AHFS categories by prior authorization, 153 (44%) required prior authorization by all MCOs.

CONCLUSIONS: The minimum formulary guidelines provided a framework for rational formulary development. All of the formularies can be generally deemed to be therapeutically sound; however, some inadequacies were noted. This type of integrated analysis of drug formularies for several MCOs provides a baseline to improve patient care through ongoing comprehensive formulary review.

Nephrology

110. Cisapride use in endstage renal disease: should it be contraindicated? Melissa J. Hentges, Pharm.D., M.B.B.S.; Minneapolis, MN.

PURPOSE: This study involves a retrospective inpatient chart review of endstage renal disease (ESRD) patients receiving hemodialysis to observe if cisapride use results in a sudden increase in heart rate (HR), QT, and corrected QT (QTC) intervals on 12-lead EKG.

METHODS: Medical records for 61 patients were obtained and reviewed. HR, QT, and QTC on all 12-lead EKGs, reason for admission, past medical history, and concomitant medications were documented. Twenty-three patients met the inclusion criteria of active hemodialysis and ≥ 2 EKGs while on cisapride and ≥ 2 EKGs while off cisapride. Statistical analysis was done using the Student's t-test.

RESULTS: A total of 528 EKGs (278 on cisapride/250 off) were included. The results, on versus off cisapride, respectively, were as follows: HR: 88 vs 84 beats/minute (p = 0.18), QT: 373 vs 382 msec (p = 0.24), and QTC: 443 vs 441 msec (p = 0.39). Overall, on cisapride, 723 patients had a significantly faster average HR; 43 patients had a significantly longer average QT and average QTC. No significant difference was found in the number of admissions/month while on or off cisapride. One patient did expire from ventricular arrhythmias shortly after discontinuing cisapride. The patient's QTC was significantly longer on versus off cisapride (487 vs 462 msec, p = 0.0066); however, the patient had experienced syncopal episodes, atrial arrhythmias and ventricular conduction problems prior to cisapride use.

CONCLUSION: This study found no significant overall difference in HR, QT, and QTC interval or admissions/month versus off cisapride. These results re-emphasize the question: should cisapride be contraindicated in ESRD patients?


PURPOSE: Conventional HD only effectively removes small molecules (MW < 500D), which are minimally protein bound. The introduction of high-flux biocompatible membranes has dramatically increased the clearance of mid-MW drugs such as vancomycin. The clearance of many commonly utilized small MW drugs, however, have not been evaluated under these dialytic conditions. This in vitro study was designed to quantify the disposition of tobramycin (MW 468D) during HD with a low flux and high flux biocompatible polymethylmethacrylate (PMMA) dialyzer.

METHOD: In vitro dialysis was performed for 3 hours using 6.0 L of phosphate buffered saline, a standard aseptic buffer was pumped through the dialyzer at 1000 to 300 mL/min to approximate a blood flow of 150 to 450 mL/min based on Hct of 34%. Dialysate flow was ~500 mL/min. Low-flux (Toray B3-2.0A) and high-flux (Toray BK-2.1U) PMMA dialyzers were evaluated. The clearance (ClD) of urea, creatinine and tobramycin was determined as the mean amount of solute recovered during two discrete dialysis collections divided by the area under the buffer concentration time curve of the intervals.

RESULTS: The sieving coefficients of urea, creatinine and tobramycin were similar between the two filters: 0.99 ± 0.06 vs 0.99 ± 0.07 for urea, and 0.99 ± 0.06 vs 0.99 ± 0.06 for creatinine (mean ± SD). The ClD (mL/min) of urea, creatinine and tobramycin between the two dialyzers was not significantly different (p > 0.05) at all three flow rates.

Flow rate (mL/min) | Urea | Creatinine | Tobramycin
---|---|---|---
Low-flux | 200 to 300 | 200 to 300 | 200 to 300
High-flux | 204 ± 10 | 205 ± 25 | 202 ± 10

CONCLUSIONS: The ClD of tobramycin by both PMMA dialyzers significantly exceeded previously reported values of 31.4 to 51.2 mL/min for ruprophene and cellulosate acetate dialyzers (Int J Clin Pharmac Ther 1987;25:50-5 and Antimicrob Agents Chemother 1984;25:128-30). The projected fraction of tobramycin removed by three hours of HD (blood flow rate = 300 mL/min) ranged from 75.5% to 83.3% for PMMA vs 26.6% to 41.9% for acetate. These findings indicate that the post-HD supplemental dose of tobramycin must be increased to 75 to 80% of the normal dose to maintain adequate therapeutic plasma concentrations when PMMA dialyzers are utilized.


PURPOSE/METHODS: In this 52-week randomized controlled trial of 605 hemodialysis patients, the effectiveness of clinical pharmacists (CP) interventions on HCT, the utilization of EPO and iron, iron stores, clinical events and patient-reported quality of life were evaluated. CPs evaluated the HCT, EPO and iron usage of treatment (TRT) and control (CTL) patients weekly. They made EPO and iron dosage recommendations at 4-6 week intervals on the basis of comprehensive pharmacodynamics modeling and iron needs assessment for TRT patients only. Age, gender, race, cause of ESRD, HCT, ferritin, TSAT, and EPO dosage was similar at baseline in the two groups. All statistical evaluations were adjusted for multiple comparisons.

RESULTS: The proportion of incented patients achieving target HCT (73.4% and 67.9%, respectively) within the first 26 weeks and the average time to achievement (10.6 ± 6.7 weeks vs 9.4 ± 6.8 weeks, respectively) were not statistically significantly different. TRT patients who achieved the target range, however, were 1.33 times more likely than CTL patients to have a HCT ≥ 33%, p < 0.001. A significant downward trend in EPO dosage (UK/kg/week) was evident after 24 weeks of study participation in the TRT group compared to the CTL group: the slope of the dose vs time relationship was -1.02 for TRT patients vs -0.07 for CTL patients (p = 0.032). The fraction of TRT patients who received IV iron and had TSATs ≥ 20% increased 1.33 fold, respectively. The total dose of IV iron administered during the study was 2369 ± 1890.9 mg in the TRT patients vs 2042 ± 1547.5 mg in the CTL patients (p = 0.0517). This may have contributed to the higher proportion of TRT vs CTL patients with TSATs ≥ 20 in quarters 2 and 4: p = 0.002 and p = 0.048. Quality of life measurements and the incidence of bleeding, hospitalizations, hypertension, and thrombosis in the TRT and CTL group were similar. The incidence of infections was the same (13.6%) during the first six months. However, it was lower in the TRT patients during the second six-months of the study. 43.6% vs 33.6%, p = 0.013. This may have contributed to the difference in EPO dosage.


PURPOSE: Drug disposition during hemodialysis (HD) is affected by several physiochemical properties, including molecular size, protein binding, lipophilicity, and ionization. Conventional HD effectively removes only small molecules which are minimally protein bound. High-flux dialysis increases the clearance of vancomycin, a prototypical middle molecule (MW = 1400D), by 8-10 fold relative to conventional HD. The purpose of this study was to ascertain if the enhanced dialytic clearance of vancomycin was associated with the ultrafiltration coefficient of the dialyzer (i.e., low vs high flux) or a property of the dialyzer membrane.

METHOD: In vitro dialysis was performed for 3 hours using 6.0 L of phosphate buffered saline. The aqueous solution was pumped through the dialyzer at 100 to 300 mL/min to approximate a blood flow of 150 to 450 mL/min based on Hct of 34%. Dialysate flow was ~500 mL/min. Low-flux (Toray B3-2.0A) and high-flux (Toray BK-2.1U) PMMA dialyzers were evaluated. The sieving coefficient (SC) and clearance (ClD) was determined via standard methods from the pre-dialyzer, post dialyzer and ultrafiltrate concentrations determined every 5-10 min during dialysis.

RESULTS: The Sc of urea and creatinine with the two dialyzers were similar: 0.99 ± 0.03 vs 0.98 ± 0.06 and 0.99 ± 0.03 vs 0.99 ± 0.05, respectively (mean ± SD). However, the SC of vancomycin with the HFD significantly exceeded the LFD value, 0.91 ± 0.14 vs 0.81 ± 0.20. The ClD (mL/min) of urea, creatinine and vancomycin increased as the flow rate increased. However, there was no significant difference; in fact, a slight decrease in HFD vs LFD at the same flow rate.
CONCLUSIONS: The $C_{\text{D}}$ of vancomycin by these PMMA dialyzers in the absence of protein binding appears to be predominantly dependent on the characteristics of the membrane (i.e., pore radius rather than the ultrafiltration coefficient). Although the molecular size of vancomycin greatly exceeds that of urea and creatinine, since these endogenous solutes are efficiently cleared with HDF and HDF, their clearance or markers thereof (KTV) may be used to individualize vancomycin therapy for HD patients.


11AE. Cefazolin and ceftazidime clearance during hemodialysis with low- and high-flux polymethylmethacrylate dialyzers. G.R. Matzke, Pharm.D., Cheng Jin Li, M.S., Anna Santos, Pharm.D.; Purdue University, Indianapolis, IN; James D. Coyle, Pharm.D.; Alan H. Lau, Pharm.D.; Mia A. Kim, Pharm.D., Kevin M. Sowinski, Pharm.D., IN; Indiana University, Indianapolis, IN.

PURPOSE: The introduction of high-flux and biocompatible membranes has dramatically increased the clearance of vancomycin (MW = 1400D). The clearance of cefazolin and ceftazidime, which are frequently utilized for the management of access and systemic infections in HD patients, however, have not been evaluated under these new dialytic conditions. This in vitro study was designed to quantify the disposition of cefazolin (MW = 455D) and ceftazidime (MW = 547D) during HD with low and high flux biocompatible dialyzers.

METHODS: In vitro dialysis was performed for 3 h using 6.0 L of phosphate buffered saline. The aqueous buffer was pumped through the dialyzer at 100 to 300 ml/min to approximate a blood flow of 150 to 450 ml/min based on Hct of 34%. Dialyze flow was ~500 ml/min. Two different PMMA dialyzers were evaluated: low-flux (Toray B3-2.0A) and high-flux (Toray B2-2.1U).

RESULTS: The sieving coefficients (SC) of all four solutes determined during isolated ultrafiltration with the high-flux dialyzer were > 0.99. The $C_{\text{D}}$ (ml/min) of urea, creatinine, cefazolin and ceftazidime by both dialyzers was flow rate dependent.

CONCLUSIONS: Since the MW of cefazolin and ceftazidime are similar and 117. Chronic hemodialysis patients’ blood pressures do not vary as a function of weekly dialysis session number. James D. Coyle, Pharm.D., Maria C. Pruchnicki, Pharm.D., William H. Bay, M.D.; The Ohio State University, Columbus, OH.

PURPOSE: To test the hypothesis that chronic hemodialysis patient blood pressure changes are similar between subsequent sessions due to eccentric intervals in thrice weekly dialysis.

METHODS: Demographic information and four consecutive weeks of pre- and post-dialysis systolic (SBP) and diastolic (DBP) BP were analyzed for all patients served by a university outpatient hemodialysis center.

RESULTS: The patient population (N=42), median age 51.5 years (range 25-84) and dialysis duration of 26 months (range 1-167), was 54.8% male, 69.0% African-American, and 28.6% Caucasian. BP data were not normally distributed and not normalized by usual transformations (Kolmogorov-Smirnov test, p<0.001); medians and nonparametric statistical tests were therefore employed. Each patient’s pre-dialysis SBP, pre-dialysis DBP, post-dialysis SBP, and post-dialysis DBP were estimated for each weekly dialysis session as the median of all corresponding observations over the study period. Median (range) BP in mm Hg for the first, second, and third weekly dialyses were:

- Pre-dialysis SBP: 146 (118-177) mm Hg
- Pre-dialysis DBP: 79 (60-95) mm Hg
- Post-dialysis SBP: 133 (103-166) mm Hg
- Post-dialysis DBP: 71 (50-99) mm Hg

BP differences among the dialysis sessions were not significant (Friedman test, p>0.05).

CONCLUSIONS: The results do not support our hypothesis, suggesting that weekly dialysis session number need not be considered when evaluating BPs in chronic hemodialysis patients. The results also suggest that medians and nonparametric tests should be used to accurately summarize and analyze BP data in these patients.

Neurology

118. Reduction in the amount of deterioration in Alzheimer’s disease patients with cholinesterase inhibitors. John Messina, Pharm.D., Richard Hartman, Ph.D., Lisa Malaty, Pharm.D.; Novartis Pharmaceuticals, East Hanover, NJ; Rutgers College of Pharmacy, Piscataway, NJ.

PURPOSE: The assessment of benefit from cholinesterase inhibitors (CHE-
Is in the symptomatic treatment of Alzheimer’s disease (AD) has been focused on their ability to improve cognition, global functioning, and activities of daily living. Since AD is a progressive, neurodegenerative disease, maintaining the current level of function or reducing worsening should be considered beneficial when assessing a treatment. The objectives of the current analysis were to determine the effects of rivastigmine on reducing the amount of worsening on: 1) cognition as measured by the Cognitive Subscale of the Alzheimer’s Disease Assessment Scale (ADAS-Cog); 2) global functioning as measured by the Clinician’s Interview Based Impression of Change with Caregiver Input (CIBIC-Plus); and 3) activities of daily living as measured by the Progressive Deterioration Scale (PDS).

METHODS: Analyses were conducted on 625 mild to moderately severe AD patients in one of the phase 3 controlled rivastigmine studies. Analyses were performed to compare the incidence of different levels of worsening of the observed cases population between the 6-12 mg/day rivastigmine group and the placebo group, and the 1-4 mg/day rivastigmine group and the placebo group at week 26 on the ADAS-Cog (0-, 4-, and 7-point decline), CIBIC-Plus (stabilized or worsened), and PDS (any worsening).

RESULTS: A greater percentage of patients receiving placebo worsened on the ADAS-Cog, CIBIC-Plus, and PDS compared to high dose (6-12 mg/day) and low dose rivastigmine (1-4 mg/day). The difference between the placebo and the 6-12 mg/day rivastigmine group was statistically significant for the 0-, 4-, and 7-point decline in the ADAS-Cog, stabilized or worsened on the CIBIC-Plus, and for any worsening on the PDS (p<0.05).

CONCLUSION: Improvement from baseline with rivastigmine on cognition, global functioning, and activities of daily living has been demonstrated in two double-blind, placebo-controlled studies. The data also show that AD patients treated with rivastigmine do not worsen on cognition, global function, and activities of daily living as much as patients treated with placebo.


PURPOSE: It has been hypothesized that elevated cholesterol may be a risk factor for dementia. A corollary to this would be that elevated cholesterol is associated with greater cognitive deficits. This study was a retrospective analysis of serum cholesterol levels and its effect on cognition in patients with mild to moderately severe Alzheimer’s disease (AD) in clinical trials with the acetylcholinesterase inhibitor, rivastigmine. The objectives were to determine if higher baseline cholesterol levels: 1) correlate with greater cognitive impairment, 2) influence cognitive decline, and 3) predict response to rivastigmine.

METHODS: Analyses were conducted on 1848 AD patients enrolled in three 26-week, double-blind, placebo-controlled rivastigmine clinical studies. Patients in the baseline cholesterol and rivastigmine group were categorized by their baseline mean total cholesterol, and comparisons of cognitive changes were based on the difference between baseline and week 26 assessments on the cognitive subscale of the Alzheimer’s Disease and Assessment Scale (ADAS-Cog).

RESULTS: ADAS-Cog scores at baseline were similar in both cholesterol groups. There was a slight difference in the mean change in ADAS-Cog scores in the placebo groups from baseline for total cholesterol (TC) ≥ 200 mg/dl or < 200 mg/dl were 11.03 and 7.81, respectively. The 2.26 point worsening was statistically significant or statistically significant difference seen in the mean change on the ADAS-Cog scores between the placebo patients in either cholesterol category. The mean TC was comparable for both responders and non-responders.

CONCLUSION: TC levels neither predicted severity of cognitive deficits nor the rate of decline in cognition over time in AD patients. Total cholesterol levels did not alter the patient’s response to rivastigmine treatment. Increased total cholesterol does not appear to be a risk factor for worsening cognition and is not predictive of AD severity.

120. Readability of printed sources of information for epileptic patients: implications for patient education. David R. Foster, Pharm.D., Denise H. Rhoney, Pharm.D.; Wayne State University; Detroit Receiving Hospital and University Health Center, Detroit, MI.

PURPOSE: Written information can be a valuable tool in patient education. Studies evaluating written information for various disease states have frequently demonstrated that the majority of written literature is written at a readability level that exceeds that of the average patient, and it has been recommended that written communications with patients should be at a fifth grade level or lower. The purpose of this study was to assess the readability of written patient information available to epileptic patients.

METHODS: One hundred one samples of written patient information were obtained from various sources, including state and national epilepsy organizations, government organizations, pharmaceutical manufacturers, the Internet, universities, pharmacy resources (Micromedex, USPD), the lay press, and medical centers (hospitals and clinics). The information was classified based on content and intended audience, and readability was assessed using the Flesch-Kincaid grade level (FKGL) as calculated by Microsoft Office. Results: The mean FKGL for all samples was 9.4. When analyzed according to content, mean FKGLs were: general disease information, 9.7; general treatment information, 11.9; drug specific information, 9.0; surgical options, 8.5; information for families, 10.6; childhood seizures, 7.2; first aid, 8.5; diet, 9.1; nonpharmacological therapy, 10.8. Mean FKGL for different sources of information were: state epilepsy organizations 10.3 (printed), 7.2 (Internet); national epilepsy organizations 8.7 (printed), 12.0 (Internet); pharmaceutical manufacturers, 7.5; government organizations (university based), 11.1; Internet (non-university/non-state or organization based), 11.0; Micromedex/USPD, 7.8; lay press, 9.3; hospitals/clinics, 8.8. Mean FKGLs for information intended for adults, adolescents and children were 6.5 and 4.1, respectively.

CONCLUSIONS: The majority of written information tested was written at a level that exceeds the reading ability of many patients. Information intended for adults may be ineffective, as it contains information written at higher grade levels, while information intended for children and adolescents may be written at levels appropriate for adults. This study emphasizes the importance of direct patient education, and the limitations of written patient information. Efforts should be taken to develop written teaching tools that target low-level readers, and we are currently working to develop better written epilepsy teaching tools at our institution.

121E. Effect of nimodipine dosage adjustments for patients experiencing hypotension after aneurysmal subarachnoid hemorrhage. Denise H. Rhoney, Pharm.D., Alison Tran, Pharm.D., Kellie R. Murray, Pharm.D., William M. Coplin, M.D.; Wayne State University; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: To evaluate the incidence of nimodipine induced hypotension in patients with aneurysmal subarachnoid hemorrhage (SAH). Secondary objectives were to: evaluate whether adjusting the dosing regimen alleviates hypotension; identify risk factors that potentiate hypotension; and evaluate the relationship between nimodipine associated hypotension and outcome.

METHODS: We reviewed random charts of patients admitted between 1996 and 1997 with SAH who received nimodipine. Study endpoints included hypotension, vasospasm, ischemic stroke, and specific outcomes. Hypotension was defined as a fall in mean arterial pressure (MAP) of ≥ 5 mm Hg, and a value < 0.05 was considered statistically significant.

RESULTS: We included 62 patients, 73% female, mean age 50 ± 15 years. Mean admission Hunt & Hess, Fischer, and Glasgow Coma Scale scores were 2(1-5), 3(1-4), and 14(3-15), respectively. Hypotension attributed to nimodipine developed in 12% (n=9) of patients; six of these seven underwent dosage adjustment to 30 mg q2h. Mean MAP changed with nimodipine 60 mg q4h from 96 ± 13 to 93 ± 15 mm Hg; however, mean MAP with the 30 mg q2h dose changed from 97 ± 20 to 85 ± 12. The only significant risk factor for development of hypotension was pre-existing cardiovascular disease (p=0.02). The mean time to onset of hypotension was 7 ± 5 days. The development of hypotension did not influence patient outcome.

CONCLUSIONS: The incidence of hypotension associated with nimodipine after SAH in our institution is 12%. The incidence and effects of hypotension may have been masked by hypertensive, hypervolemic therapy. The only risk factor found was the presence of preexisting cardiovascular disease. Dosage reduction did not alleviate nimodipine induced hypotension and had very little impact on the patient’s overall outcome.

Presented at the 51st Annual Meeting of the American Academy of Neurology, Toronto, ON, Canada, April 17-24, 1999.

Oncology

122. Societal costs of high-dose chemotherapy in women with breast cancer. Jeffrey W. Hui, Pharm.D., Gary C. Yee, Pharm.D., FCCP, Raafat A. Seefeldin, M.S., Pharm.D., Ph.D., Renee Boyette, B.S.N., James C. Lynch, Ph.D., John R. Wingard, M.D.; University of Nebraska Medical Center, Omaha, NE; University of Florida; Shands Hospital, Gainesville, FL; G.D. Searle, Chicago, IL.

PURPOSE: The purpose of the study was to determine the economic burden of high-dose chemotherapy (HDC) followed by hematopoietic stem cell transplantation in 100 women with breast cancer.

METHODS: Clinical and resource utilization data were collected prospectively from the pre-transplant work-up and continuing for 30 days following discharge in patients treated at six U.S. transplant centers. Resource units were converted to costs based on Shands databases and Medicare fee schedules. Caregiver time and out-of-pocket costs were collected from interviews pre- and post-transplant.

RESULTS: Results from 66 women (median age: 50 years) with stage II (n=27), III (n=22), or IV (n=27) disease have been analyzed. Eleven patients had autologous transplant complications: one patient died from a second transplant from renal and respiratory failure and sepsis. Median times to neutrophil and platelet recovery were 11 and 17 days, respectively. Mean...
123. Assay development and interim pharmacokinetic analysis of Karenitecin: a novel highly lipophilic camptothecin derivative. Judith A. Smith, Pharm.D., Fred Haushaefer, Robert Newman, Ph.D., Timothy L. Madden, Pharm.D., University of Texas M.D. Anderson Cancer Center, Houston, TX; BioNumerik Pharmaceuticals, Inc., San Antonio, TX.

PURPOSE: Determine the clinical pharmacokinetics of IV karenitecin, a novel supercomputer engineered highly lipophilic camptothecin derivative.

METHODS: Blood and urine samples were obtained from phase I patients with solid tumors receiving escalating doses of karenitecin, administered daily x 5 consecutive days as a 60 minute infusion every 21 days. The starting dose level was 0.15 mg/m² with escalation to 0.3, 0.6, 1.2 and 2.4 mg/m² by accelerated dose titration until dose-limiting toxicity (DLT) was observed. Samples were obtained on days 1-5 at numerous timepoints. The samples were analyzed for karenitecin by HPLC. Compartmental models were fit to the plasma and urine concentration time data using ADAPT II.

RESULTS: Six patients enrolled in the study have had pharmacokinetic (PK) data analyzed to date. First course DLT (myelosuppression - expected) was reached at 2.4 mg/m². A 2-compartment model best describes the plasma data analyzed to date. Samples were obtained on days 1-5 at numerous timepoints. The samples were analyzed for karenitecin by HPLC. Compartmental models were fit to the plasma and urine concentration time data using ADAPT II.

CONCLUSIONS: The minority of patients with AML have neutralizing antibodies against DT₃₈₈-GMCSF. Future work will correlate an ELISA assay with their bioassay results. We have initiated a phase I trial of DT₃₈₈-GMCSF in relapsed AML patients and will determine if neutralization of DT₃₈₈-GMCSF in this assay correlates with response or altered pharmacokinetics.

126. The comparison of lenograstim and filgrastim on autologous peripheral blood stem cell transplantation patients with high-dose chemotherapy. In Hyang Kim, M.S. candidate, Jung Mi Oh, Pharm.D., Sung Kyu Park, M.D., Sookmyung Women's University; Soonchunhyang University Hospital, Seoul, Korea.

PURPOSE: High-dose chemotherapy following autologous bone marrow transplantation is a therapeutic option for patients with chemotherapy-sensitive malignancies who have relapses. Hematopoietic growth factors are accepted as accelerating hematopoietic recovery after bone marrow grafting. The comparison of two different recombinant granulocyte colony-stimulating factors (G-CSF), lenograstim (glycosylated) and filgrastim (nonglycosylated) was performed.

METHODS: The comparison of two different recombinant granulocyte colony-stimulating factors (G-CSF), lenograstim (glycosylated) and filgrastim (nonglycosylated) was performed in 85 patients after peripheral blood stem cell transplantation (PBSCT) following high-dose chemotherapy (HDCT) to compare the effects of different forms of G-CSF. One day after stem cell infusion, 49 patients received filgrastim 250 µg per day, and 36 patients received filgrastim (non-glycosylated) 300 µg per day.

RESULTS: ANC recovery to above 500/mm³ for three consecutive days was earlier in filgrastim-treated group than lenograstim group (19.0 ± 10.0 vs 13.2 ± 7.7; p=0.004). Time to WBC recovery above 4000/mm³ was earlier in filgrastim-treated group than lenograstim group (29.9 ± 16.6 vs 16.9 ± 9.7; p=0.001). The difference of platelet recovery was significant in filgrastim-treated patients (27.2 ± 3.8 vs 19.5 ± 11.6; p=0.006). Furthermore, filgrastim-treated patients received fewer days of antibiotic administration and spent less time in hospital. However, days of neutropenic fever, kinds of antibiotics and transfusion times were similar in both groups. There was no significant drug-related toxicity associated to both groups.

CONCLUSION: In patients undergoing autologous PBSCT following HDCT for neoplastic disease, filgrastim significantly reduced duration of neutropenia and led to earlier hospital discharge than lenograstim in this study.


PURPOSE: To assess compliance of empiric antibiotic therapy to the 1997 Infectious Diseases Society of America (IDSA) guidelines for febrile neutropenia (FN). Selected outcomes for compliant and non-compliant therapy were evaluated.

METHODS: A concurrent, non-interventional chart review of 50 consecutive episodes of FN between January and May 1999 at a university-affiliated, tertiary referral oncology centre was conducted. Empiric antibiotic therapy was assessed for compliance relative to the IDSA guidelines. Determine the infection and response to therapy were assessed with previously published criteria.

RESULTS: An empiric regimen compliant to the guidelines was prescribed in 28/50 episodes (56%). Hematological malignancy constituted a greater percentage of the compliant than noncompliant group (75% vs 50%; p<0.001). There was no significant difference between compliant and
noncompliant episodes with respect to the following: number of microbiologically-defined infections, defervescence at 72 hours, number of antibiotic modifications, response to therapy, duration of the empiric regimen, number of adverse reactions necessitating a regimen modification, admission to the intensive care unit and mortality. The mean duration of antibiotic therapy, time to discharge from the onset of FN and the number of infections during treatment were greater for children receiving CRCl compared to non-compliant episodes (p<0.02, p=0.04, p=0.005, respectively).

CONCLUSION: Compliance to IDSA guidelines for empiric antibiotic therapy of FN was 56%. Episodes of FN associated with hematological malignancies were most often compliant prescribed CRCl empiric antibiotic therapy. Results do not suggest the need for a widespread prescriptive policy enforcing compliance to the guidelines for all episodes of FN at our oncology centre.


PURPOSE: This study evaluated the predictive performance of four methods for estimating creatinine clearance (CrCl) in patients with ovarian cancer: Cockcroft and Gault, and two equations derived in cancer patients, Robinson, et al. and Tsukabi, et al.

METHODS: Estimated CrCl values obtained by each method using actual weight, ideal weight, and low and non-compliant equations were compared with measured values determined by 24-hour urine collection for 14 patients. Linear regression and correlation analysis was performed to assess the relationship between predicted and measured CrCl. The mean prediction error (MPE) and mean absolute error (MAE) were calculated to evaluate the bias and precision, respectively, of each method.

RESULTS: The relationship between predicted and measured CrCl is fair (r=0.39 to 0.55). Cockcroft and Gault using ABW (p=0.21), Robinson using ABW (p=0.44), and jelliffe (p=0.17) were equally unbiased predictors of measured CrCl. All other methods significantly underestimated measured CrCl. All methods appeared to be equally imprecise (p<0.05).

The use of oncology specific equations did not improve on the accuracy or precision of these estimates.

129. Clinical experience of bone mineral density scanning in children with osteogenesis imperfecta: A retrospective review. Jennifer H. Justice, Pharm.D., Philip E. Empey, Pharm.D., Margaret K. Winkler, M.D., Robert J. Kuhn, Pharm.D.; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: While bone mineral density (BMD) scanning has been widely studied in adults, there is little data to support its use in pediatric patients. This retrospective chart review is to assess the usage pattern of BMD scanning in children's hospital and develop guidelines for the administration of this agent to pediatric patients at our institution.

METHODS: We report the management of thromboembolic events in nine infants; all were admitted to the children's hospital from July 1998 through February 1999. Demographic data, indication for use, dates of therapy, dosing regimen, outcome of therapy and outcome of adverse drug reactions were recorded. All data were analyzed with the Wilcoxon rank-sum test. Values and radiologic studies were recorded to assess the average dose and regimen, outcomes of therapy and frequency of adverse drug reactions.

RESULTS: Nine patients were treated with t-PA at our institution over an 8-month period. The average age was 3 months (range 6 days-19 months) with a weight of 3.4 kg (range 815 g-10.4 kg). Indications for the use of t-PA included arterial and venous thrombosis, BT-shunt and catheter-related clots, SVC syndrome, and pulmonary veno-occlusive disease. Sixteen courses of therapy with an average dose of 0.2 mg/kg/hr for 6.25 hours were administered. Clot improvement/resolution was observed in 89% of patients. Concurrent therapy included enoxaparin (4/9), heparin (1/9), and fresh frozen plasma (5/9), with no serious adverse events reported.

CONCLUSIONS: The use of t-PA aids in clot resolution with a low incidence of adverse effects. Based on our experience, we are currently recommending 0.3 mg/kg/hr for 6 hours until more definitive data is available.

130. The study on efficacy and safety of deflazacort in Korean children with nephrotic syndrome. Mijung Kim, M.S., Dong Kyu Jin, M.D., Ph.D., Sukhynag Lee, Pharm.D., M.S.; Sookmyung Women’s University; Samsung Medical Center; Sungkyunkwan University, Seoul, Korea.

PURPOSE: To study efficacy and safety of deflazacort in children with nephrotic syndrome. Deflazacort, an oxazoline derivative of prednisolone, has been claimed to have anti-inflammatory effects with few side effect profiles compared to prednisone.

METHODS: Patients were eligible when the children with nephrotic syndrome were treated with deflazacort at Samsung Medical Center, Seoul, Korea, from October 1994 to April 1999. The nephrotic syndrome was defined as less than 2.5 mg/dl of albumin level and more than 40 mg/m2 BS/ahr of protein excretion in 24-hour urine. The exclusion criteria were the secondary nephrotic syndrome due to systemic lupus erythema, chronic renal failure, multiple myeloma and a primary parameter of deflazacort to treat nephrotic syndrome were response rate, frequency of relapse and time to respond. The safety profiles assessed were the impact on children’s growth, calcium sparing effect, glucose metabolism and lipid profile by comparing before treatment. Adverse drug reactions associated with deflazacort were evaluated.

RESULTS: The median time to respond was 12 days (7-110 days) and frequency of relapse was 1 (0-6). The change of plasma calcium was from pre-therapy of 7.55 ± 3.86 mg/dl to post-treatment level of 9.98 ± 3.77 mg/dl (p<0.0001), but phosphate level was not significantly changed (5.02 ± 0.67 mg/dl vs 5.04 ± 0.75 mg/dl, p>0.05). Weight/height ratio was increased from 22.05 ± 3.47 kg/m2 to 23.34 ± 3.44 kg/m2 (p<0.001). The fasting blood glucose level was not significantly changed (91.92 ± 5.53 vs 98.19 ± 4.78 mg/dl, p=0.072) while the change of total cholesterol was significant (362.3 ± 12.0 vs 254.1 ± 11.5 mg/dl, p<0.0001).

CONCLUSIONS: Deflazacort had similar efficacy compared to prednisone with less impact on growth inhibition and metabolic side effects of hyperglycemia and hyperlipidemia in treatment of children with nephrotic syndrome.

131. The use of methadone to prevent fentanyl withdrawal in the pediatric intensive care unit. Ralph A. Lugo, Pharm.D., Robert MacLaren, Pharm.D., Jared Cash, B.S.; University of Utah; Primary Children's Medical Center, Salt Lake City, UT.

PURPOSE: Prolonged administration of fentanyl often results in opioid dependence in critically ill children and rapid discontinuation may precipitate opioid abstinence syndrome (OAS). Transitioning to low-dose enteral administered methadone in advance of fentanyl discontinuation may reduce the risk of OAS. In addition, methadone’s long half-life may simplify the taper schedule. The objective of this retrospective study was to evaluate and describe the use of methadone to expedite fentanyl discontinuation and prevent signs/symptoms of withdrawal in children in the PICU.

METHODS: PICU clinical guidelines for initiating enteral methadone (via nasogastric tube) and rapidly discontinuing fentanyl in children at risk for OAS were implemented 3 years prior to data collection. All PICU patients during the 3-year period who were at high risk for OAS (9 ≥ days of continuous fentanyl infusion) were included in the study. Medical records were reviewed for fentanyl/methadone utilization and collected signs/symptoms of withdrawal. OAS was defined as ≥ 3 predetermined signs/symptoms of withdrawal occurring within 72 hours of fentanyl/methadone dose reductions.

RESULTS: Twenty-two patients were included in the analysis (mean age 6.1 ± 5.4 years). Duration of continuous fentanyl administration = 17.8 ± 8.4 days; peak infusion rate = 5.9 ± 3.8 μg/kg/hr; median infusion rate 24 hours before rapid fentanyl discontinuation = 4.8 μg/kg/hr. Methadone (0.50 ± 0.22 mg/kg/day) was initiated 1.0 day (median) prior to rapid fentanyl discontinuation. Fentanyl was discontinued in 2.6 days (median) and 21/22 patients had no documented OAS. The single patient with OAS required increased doses of fentanyl/methadone. Methadone was tapered in 18.2 ± 11.9 days with no OAS (n=22).

CONCLUSIONS: The use of enteral methadone facilitates rapid discontinuation of fentanyl and may prevent OAS in children at high risk for fentanyl withdrawal.

132. Pharmacokinetics/pharmacodynamics of omeprazole suspension in critically ill pediatric liver/intestinal transplant patients. Kimberly L. Bergman, Pharm.D., Stuart Kaufman, M.D., Dean Collier, Pharm.D., Jill A. Rebuck, Pharm.D., Keith M. Olsen, Pharm.D., FCCP; University of Nebraska Medical Center, Omaha, NE.

PURPOSE: This study characterized the pharmacokinetics and pharmacodynamics of omeprazole suspension in critically ill pediatric liver/intestinal transplant patients.

METHODS: Eleven pediatric liver and/or intestinal transplant patients were administered omeprazole suspension 0.5 mg/kg every 12 hours via nasogastric tube within twelve hours of transplantation. Gastric pH was monitored continuously for 48 hours via a single channel pH probe, and sequential initial and multiple dose blood samples were obtained for determination of plasma omeprazole concentrations via HPLC. Data are expressed as means ± SD.

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RESULTS: Eleven subjects (age 3.6 ± 4.0 years; range 18 weeks to 14 years) were studied. Baseline pH was 1.0 ± 0.8, and onset of omeprozole action (time to pH > 4.0) was 62 ± 84 minutes (range 2 to 226 minutes). Percentage of the dosage interval for which pH > 4.0 was 78.8 ± 18.9% and 97.8 ± 5.4% upon first and multiple doses, respectively. Pharmacokinetic parameters were measured upon first and multiple doses. Pharmacokinetic parameters were measured.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)*</td>
<td>812.6 ± 549.1</td>
<td>1258.7 ± 2286.2</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.2 ± 0.8</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>AUC0-24 (ng•h/ml)*</td>
<td>3818.1 ± 2274.5</td>
<td>6000.6 ± 2361.1</td>
</tr>
<tr>
<td>AUC0-24 (ng•h/ml)*</td>
<td>4956.3 ± 1300.5</td>
<td>7622.9 ± 2738.0</td>
</tr>
<tr>
<td>Vd (l)</td>
<td>4.9 ± 3.5</td>
<td>5.1 ± 2.4</td>
</tr>
</tbody>
</table>

P<0.05

CONCLUSIONS: Although onset of action of omeprozole suspension was highly variable in this study population, omeprozole adequately maintained baseline and mean gastric pH greater than 4.0 throughout the dosage interval upon multiple doses in a pediatric liver/intestinal transplant population.

133. Case study control of corrected QT intervals in premature infants treated with cisapride. Corey S. Cuthrell, Pharm.D., Christopher M. Rubino, Pharm.D., J. Laurence Ransom, M.D., McCrae Smith, M.D., Rita Carlos, M.D., Andrew Davey, M.D., Annanic Dimagula, M.D., James Pascale, M.D., Peter Gal, Pharm.D., Greensboro Area Health Education Center, Moses Cone Health System, Greensboro, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC.

PURPOSE: Secondary to the recent warning that cisapride may cause corrected QT interval (QTc) prolongation in neonates, results of electrocardiograms (ECG) were compared between patients receiving cisapride and those who were not.

METHODS: Our computerized neonatal patient database was used to identify all patients born between April 1997 and May 1999 who received cisapride (CIS) for gastroesophageal reflux with an ECG during therapy. Each CIS patient was matched to two controls (CON) who had received an ECG some time during hospitalization. Cisapride dosing history was collected for the CIS patients and QTc intervals and dates of the ECGs were collected for both groups. Presence of electrolyte abnormalities and concurrent medications known to alter QTc were recorded for both groups.

RESULTS: Forty nine patients were evaluated. Fifteen CIS vs 30 CON. There was no statistically significant difference in the median QTc in CIS versus CON patients (410 vs 416, respectively; p=0.38). Nine of the 45 patients had a prolonged QTc ≥ 450 msec (2/15 CIS vs 7/30 CON). Univariate analysis showed no correlation between the dose or duration of cisapride prior to the ECG and the maximum QTc. For 6/7 CON, potential causes of prolongation were identified (electrolyte abnormalities, dexamethasone use, and diuretic use) and no causes other than cisapride were found in the two CIS patients with increased QTc. In the CON group, there were no differences in gestational age or weight, or predilation for those with prolonged QTc intervals although CON patients with hypocalcemia were more likely to have prolonged QTc intervals than those with normal calcium levels (43% vs 17%, respectively). In CON patients, ECGs were performed once a day during therapy, 10% of CON patients had hypocalcemia.

CONCLUSIONS: Cisapride is an acceptable etiology for prolonged QTc intervals in premature infants. In the absence of concurrent interacting drugs, however, cisapride does not seem to place infants at higher risk for proarrhythmias than their control counterparts.

134. Granulocyte colony-stimulating factor serum and urine concentration in neonpic neutropenia before and following the intravenous administration of recombinant G-CSF. Darlene A. Calhoun, D.O., Amanda M. Rauck, M.D., Frederick B. Ruymann, M.D., John Koepke, Pharm.D., Diane Davis, B.S.N.; Ohio State University; Columbus Children’s Hospital, Columbus, OH.

PURPOSE: To evaluate individualized pharmacokinetic (IPD) versus nomogram dosing (ND) of gentamicin among neonatal intensive care unit (NICU) patients.

METHODS: A multicenter, retrospective chart review of all patients admitted to the NICU from November 1, 1997 to November 1, 1998 was performed. Patients receiving gentamicin within the first 10 days of life were included and received either ND of 2.5 mg/kg/dose with dosing intervals based on gestational and postnatal age or IPD based on a 5 mg/kg load with subsequent doses and intervals based upon individualized pharmacokinetic analysis of serum concentrations obtained with the loading dose. Information collected for all patients included gestational age, birth weight, 1 and 5 minute Apgar scores, perinatal and current disease states, concurrent medications, renal function, and gentamicin dosing history including concentrations.

RESULTS: Two hundred fifty patients were evaluated: 65 IPD (Greensboro) vs 185 ND (Omaha/Miami). Demographic characteristics were comparable between the two groups. Sixty-five percent of patients receiving IPD had initial peak gentamicin concentrations > 8 mg/L compared to 17% of patients on ND (<0.001). In addition, trough concentrations exceeding 2 mg/L were reported in 38% of patients receiving ND compared to none in IPD group (p<0.001). Forty percent of patients receiving ND had higher dosage adjustments versus 10% of IPD (p<0.01). The average number of concentrations obtained per patient for ND was 2.5 versus 2.2 for IPD.

CONCLUSIONS: Compared to ND, IPD of gentamicin in patients admitted to the NICU allows for rapid achievement of desired gentamicin serum concentrations, potential for less toxicity, and a decreased number of dosing changes.
137. Angiotensin converting enzyme inhibitor use in pediatric patients with dilated cardiomyopathy. Linda K. Ohri, Pharm.D., Christopher L. Shaffer, PharmD, BCPP, Jon K. Izumi, Leiland T. Nogawa; Creighton University; Children’s Hospital, Omaha, NE.

PURPOSE: This retrospective study documented use of angiotensin converting enzyme inhibitors (ACEIs) in pediatric patients with dilated cardiomyopathy (DC).

METHODS: Review of pediatric cardiology clinic charts identified 19 patients (group A) treated with captopril or enalapril between January 1987 and May 1999. Charts for 11 age/gender/DC matched no ACEI patients (group B) were compared to a subgroup (A1) of 11 ACEI patients. Demographic, medical history, ACEI regimen, concurrent therapy, test result, and outcome data were documented.

RESULTS: At initiation of ACEI therapy ranged from 8 days to 17 years. Seventeen patients received captopril. The mean initial/maintenance doses of captopril were 1.1/1.0 mg/kg/d (range: 0.2/0.1 to 2.9/2.7 mg/kg/d) BID or BID. Six patients received a mean dose of 0.5 mg/kg IV every 3 to 4 hours. Nine patients achieved gastric pH control determined by noncompartmental methods. Concentrations were measured by HPLC and pharmacokinetics were determined by noncompartmental methods. Shortening fractions (SFs) increased in 61% of evaluable ACEI patients. Subgroup analysis showed a SF increase in 50% (5/10) of group A1 compared to 12.5% (1/8) of group B patients. Overall status improved in 47% of group A, 36% of group A1, and 0% of group B patients. Those in group A1 eventually received heart transplant. The additional treated infant died awaiting transplant. ACEIs were well tolerated.

CONCLUSIONS: ACEI therapy was initiated in patients with relatively severe dilated cardiomyopathy, and was associated with improvement or stabilization of the SF for all treated patients.

138E. Ranitidine pharmacokinetics and concentration-related control of gastric pH in critically ill children. Ralph A. Lugo, Pharm.D., A. Marc Harrison, M.D., John Sweeney, B.S., Jared Cash, B.S., Donald D. Vernon, M.D.; University of Utah; Primary Children’s Medical Center, Salt Lake City, UT.

PURPOSE: Maintaining gastric pH >4 reduces the risk of stress ulceration in critically ill patients. We analyzed ranitidine pharmacokinetics in critically ill children in the PICU and determined the plasma concentrations associated with a gastric pH >4 for greater than 75% of a 24-hour period.

METHODS: Children ≥ 10 kg who required IV ranitidine for stress ulcer prophylaxis were prospectively studied. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, and 8 hours after 2 mg/kg IV ranitidine. Following the final blood draw, the ranitidine infusion was stopped and a ranitidine followed by 0.1 mg/kg/hr infusion. Gastric pH was measured hourly via NG pH probe. For low gastric pH (pH < 4 on 6 hourly occasions in previous 24 h), 0.5 mg/kg IV ranitidine was administered and the infusion was increased by 0.05 mg/kg/hr. This sequence was repeated until gastric pH was ≥ 4 for >25% of a 24-hour period. Steady-state plasma concentrations were measured. Plasma concentrations were measured by HPLC and pharmacokinetics were determined by noncompartmental methods.

RESULTS: Since 1988, we have treated children (median 8.7 years and 30 kg) who were enrolled. PK parameters were t1/2a=31 ± 1.5 hours; C1 = 8.93 ± 3.72 ml/kg/min; VDss = 2.4 ± 1.8 L/kg. Nine patients achieved gastric pH control (6.0 ± 0.5) with ranitidine 0.17 ± 0.07 mg/kg/hr and a steady-state plasma concentration of 123 ± 22 ng/ml. Plasma concentration associated with gastric pH > 2.7 (± 0.9) was 206.9 ± 100 ng/ml.

CONCLUSION: We conclude that ranitidine pharmacokinetics are variable in critically ill children. Gastric pH > 4 is associated with a mean steady state concentration of 291 ng/ml. This concentration may be achieved with IV ranitidine 0.7 mg/kg followed by 0.15 mg/kg/hr continuous infusion or intermittent intravenous administration of 1.5 mg/kg every 6 hours. Published in Crit Care Med 1999;27:A149.

139. Risperidone versus placebo for conduct disorder in mentally retarded children. Michael G. Aman, Ph.D., Robert Findling, M.D., Martin Brecher, M.D.; Nisonger Center, Columbus, OH; University Hospital Psychiatry, Cleveland, OH; Janssen Pharmaceuticals Research Foundation, Titusville, NJ.

PURPOSE: This randomized, double-blind study compared risperidone and placebo in the outpatient treatment of conduct disorder in children with mild to borderline mental retardation.

METHODS: After a 1-week placebo run-in, 118 children aged 5 to 12 years with a diagnosis of conduct disorder were treated with placebo or risperidone each morning for 6 weeks. Doses could be adjusted within a range of 0.02 to 0.06 mg/kg/day. The primary efficacy instrument was the conduct disorder subscale of the Nisonger Child Behavior Rating Form (N-CBRF), from which change from baseline to endpoint was calculated. Secondary efficacy variables included other subscales of the N-CBRF, the Behavior Problems Inventory, and the Clinical Global Impression. Safety assessments were based on reported adverse events.

RESULTS: Statistical significant differences favoring risperidone over placebo were observed from week 1 through week 6 and at endpoint for the primary efficacy variable. Significant differences favoring risperidone were also observed for the secondary variables. Adverse events were reported in 54 of the 55 risperidone patients and in 44 of the 63 placebo patients. No serious adverse events were reported. In the risperidone group they included somnolence in 51%, headache in 29%, vomiting in 20%, dysphoria and weight increase each in 15%, hyperprolactinemia in 13%, and increased appetite and rhinitis each in 11%. Treatment was discontinued in 2 patients in the risperidone group (somnolence and somnolence plus dysphoria in 1 each).

CONCLUSION: Risperidone effectively and safely improves conduct disorder in mentally retarded children.

Pharmaceconomics

140. Clinical pharmacy services, pharmacist staffing, and drug costs in U.S. hospitals. C.A. Bond, Pharm.D., FASP, FCP, Cynthia L. Raehl, Pharm.D., FASP, Todd Franke, Ph.D.; Texas Tech University-Health Sciences Center, Amarillo, TX; University of California at Los Angeles, Los Angeles, CA.

PURPOSE: This study evaluated the associations between clinical pharmacy services, pharmacist staffing, and drug costs in U.S. hospitals.

METHODS: A database was constructed from the American Hospital Association’s Abridged Guide to the Health Care Field and the National Clinical Pharmacy Services Database. A multiple regression analysis, controlling for severity of illness, was employed to determine the associations.

RESULTS: Study population = 934 hospitals. Four clinical pharmacy services were associated with lower drug costs: in-service education (p=0.016), drug information (p=0.015), drug protocol management (p=0.049), and medication admission histories (p=0.011). Additionally, as staffing increased for hospital pharmacy administrators (p=0.0001), dispensing pharmacists (p=0.0001), and pharmacy technicians (p=0.001), drug costs increased. As staffing increased for clinical pharmacists, drug costs decreased (p=0.018). Drug costs per hospital per year were lower when these 4 clinical pharmacy services were present: in-service education $77,879.19 (a total of $48,518,735 for the 623 hospitals offering this service), drug information $430,579.84 (a total of $90,852,356 for the 211 hospitals offering this service), drug protocol management $137,333.67 (a total of $45,045,443 for the 211 hospitals offering this service), and medication admission histories $213,388.21 (a total of $5,548,093 for the 26 hospitals offering this service).

CONCLUSION: The results of this study suggest that increased staffing levels of clinical pharmacists and some clinical pharmacy services may reduce hospital drug costs.

141. Pharmacist management of diabetes and hyperlipidemia: comparison to other primary care providers in a community family practice office. Gordon A. Ireland, Pharm.D., Talonna M. Iser, Pharm.D.; Shore Health System; University of Maryland, Easton, MD.

PURPOSE: To study the documented outcomes data of patients treated for diabetes and/or hyperlipidemia in a community family practice office in order to 1) determine the clinical effectiveness of pharmacist disease management interventions, 2) determine the cost-effectiveness of pharmacist disease management interventions, and 3) evaluate effect of pharmacist disease management on physician time.

METHODS: The medical records of 217 patients, matched for age and gender, were reviewed. The HgA1c, total cholesterol, LDL, triglycerides, HDL values, and number of office visits were collected for the period of January 1 to December 31, 1998. These numbers were compared between the 4 practitioners.

RESULTS: Patients managed by the pharmacist had more severe disease (p<0.05) but reached outcome goals, HgA1c <7, total cholesterol <200, LDL <160, LDL <130, LDL <100, HDL >35, and triglyceride <200, similar to or better than the other practitioners. Mean change in HgA1c, and LDL was significant (p<0.05) when compared to the other practitioners. Pharmacists/nurse practitioner saw patients less frequently when seen by the pharmacist (p<0.05). Pharmacist intervention saved an average of $600 per patient per year.

CONCLUSION: Given the harder-to-manage and noncompliant patients, the pharmacist achieved outcomes equal to 1 practitioner and better than 2 practitioners. Significant diversity was noted between practitioners. The pharmacist interventions saved practitioner time and were clinically cost effective.

142. Patient valuation of a pharmacist provided asthma management program using the contingent valuation method. Karen Blumenschein, Pharm.D., Magnus Johannesson, Ph.D., Beth Miller, M.D.; University of Kentucky, Lexington, KY; Stockholm School of Economics.

PURPOSE: This study utilized the contingent valuation approach to benefit-cost analysis to assess the patient perceived value of a pharmacist provided asthma management service.

METHODS: Patients with asthma were recruited from an asthma specialty program using the contingent valuation method. Key actors: K. Blumenschein, M. Johannesson, and B. Miller.

CONCLUSION: The contingent valuation approach to the evaluation of pharmacist provided asthma management service was effective.

PURPOSE: Patient adherence to pharmacotherapy in clinical trials may differ from actual clinical practice, influencing the generalizability of trial data. Number-needed-to-treat (NNT) calculations for cardiovascular endpoints are available for primary prevention (WOSCOPS, NEJM 1995;333:1301) with pravastatin (P) and secondary prevention (4S, Lancet 1994;344:1383) with simvastatin (S). We recalculated NNT values to reflect actual patient adherence using Medicaid claims.

METHODS: Continuously enrolled Medicaid recipients who initiated P or S during the study period (May 1992 to January 1999) were included in the study. We defined adherence as mean patient-months (MP-M) on P or S and drug discontinuation as no prescriptions filled for 90 days. MP-M were 58.8 and 64.8 for WOSCOPS and 4S, respectively. Medicaid data were utilized to calculate new NNTs:

\[
\text{MP-M}_{\text{Medicaid}} \times \text{NNT}_{\text{Literature}} = \text{NNT}_{\text{Medicaid}}.
\]

RESULTS: During the study period, 458 and 362 patients received P and S, respectively. Patients received a mean of 23.3 mg of P and 17.5 mg of S. MP-M on therapy was 14.4 (± 16.2) and 17.1 (± 16.5) for P and S, respectively. Therefore, NNTs for myocardial infarctions were adjusted to 163 for WOSCOPS (from 40) and to 61 for 4S (from 16). Total mortality NNTs were adjusted to 453 for WOSCOPS (from 111) and 114 for 4S (from 30).

CONCLUSIONS: Medicaid patients do not appear to receive adequate doses or duration of P and S. Generalizing NNT data from clinical trials to this population may overestimate expected treatment benefits because of the observed decrease in patient adherence.

144. Costs and benefits of buprenorphine in a smoking cessation program. Michael T. Halpern, M.D. Ph.D., Zoba M. Khan, Ph.D., Carmelina Battista, Pharm.D., Terri L. Young, Ph.D.; Bethesda, MD.

PURPOSE: While cessation programs are generally cost-effective, the short-term costs and benefits of covering prescription smoking cessation aids from the perspective of an employer or health plan are often unknown. In order to quantify the economic and health care outcomes from smoking cessation programs incorporating bupropion, we developed a user-friendly computer model called Return On Smoking Cessation Opportunity (ROSCO).

METHODS: ROSCO evaluates the costs and outcomes of covering versus not covering prescription smoking cessation aids by an employer or health plan. Users specify the population size, geographic location, and category of their worksite/health plan; defaults for all other parameters are present. The model called Return On Smoking Cessation Opportunity (ROSCO).

RESULTS: Modeled costs were $7789 for NQMI, and $457 for a bleed. The PURSUIT net expense was $658,200 ($850/patient), $32,900 cost per infarction saved (CIS). The PURSUIT net expense was $6,103,000 ($1300/patient), $145,300 CIS.

CONCLUSIONS: GP IIb/IIIa inhibitors are cost-effective in reducing infarction compared to other medical interventions, but do not lead to actual cost savings.

146. Comprehensive sickle cell pain management program impact on the length of stay and readmissions for sickle cell crisis. Ru-Ming Fan, Pharm.D., M.P.H., Mark Levin, M.D., Song Ja Shin, M.S.; Brookdale University Hospital and Medical Center, New York, NY.

PURPOSE: The purpose of this study is to evaluate the effectiveness of the program/clinical guidelines for pain management for patients with sickle cell crisis. The outcome of effectiveness is defined as decreasing the length of stay (LOS) and number of times of re-admission.

METHODS: A retrospective cohort study was conducted by review of the medical records of sickle cell crisis patients at the Brookdale University Hospital and Medical Center. Due to seasonal variation with respect to the manifestation of pain in sickle cell disease patients, cases (n=66) were selected from November 1, 1997 to October 31, 1998 and controls(n=56) were selected from November 1, 1996 to October 31, 1997. The comprehensive program/clinical guidelines for pain management were implemented on November 1, 1997. Cases and controls were matched by month of admission, sex, age, race, and the severity of the pain when the patients were admitted to the hospital. Multivariate logistic regression model was used to demonstrate the significance of some factors such as infections, co-morbid illness, analgesic regimen, and the specialty of physicians for the prolongation of length of stay.

RESULTS: Cases were selected after implementation of the program with average LOS of 4.6 days and 1.3 times re-admission per patient. Controls were selected prior to implementation of the program/clinical guidelines with average LOS of 7.8 days and 2.6 times re-admission per patient. The results from multivariate logistic regression model demonstrated that the patients diagnosed with infections such as pneumonia or UTI were more significantly increased their risk of readmissions (RR = 4.5, 95% CI: 7.5 - 22.7, p<0.05), all had statistical significance with prolongation of the length of stay.

CONCLUSIONS: Due to the hospital’s geographical location, many sickle cell disease patients were admitted to the hospital. Implementation of the comprehensive pain management program/clinical guidelines to decrease the LOS and number of times re-admission per patient and the results demonstrated that the program is successful to reduce hospital readmission by use patients with sickle cell crisis.


PURPOSE: A challenge in evaluating the cost of treating cardiovascular disease in a clinical trial setting is that a method for determining the actual cost of items and services incurred in the trial is not readily available. We describe a methodology to assign inpatient costs to major cardiovascular events using a uniform approach based on publically available data sources. METHODS: For hospital costs, the 1997 Medicare Provider Analysis Review average allowed charges for cardiac diagnostic related groups were converted to costs using the national median cost-to-charge ratio and updated to 1999 using the Medicare Payment Advisory Commission’s hospital operating payment update framework. The 1997 Medicare physician fee schedule global payment update framework. The 1999 Medicare physician fee schedule global payment update framework.
RESULTS: Total costs for medical admissions ranged from $3388 for angina (no complications) to $8997 for acute myocardial infarction (complications). Costs for surgical admissions ranged from $6086 (cardiac catheterization, no complications) to $44,587 (CABG plus PTCA).

CONCLUSIONS: This study demonstrates a reproducible method for assigning inpatient hospital costs for cardiovascular events using publicly available hospital charge data. This approach may be used by those conducting economic analyses of cardiovascular disease and would allow for comparison of costs with other studies using a similar approach.

148E. Use of atypical antipsychotics in a Veterans Administration Medical Center. Matthew A. Fuller, Pharm.D., Jonathan Laich, B.S., Louis Stokes Cleveland VA Medical Center.

PURPOSE: Records of all patients treated with clozapine, risperidone, olanzapine, or quetiapine during 1998 in the Cleveland VA Medical Center were reviewed to assess concurrent medication use, length of stay, hospital admissions, and costs of treatment.

RESULTS: Clozapine was received by 145 patients, risperidone by 636, olanzapine by 395, and quetiapine by 40. The patients’ mean ages ranged from 49 to 54 years; 90% were men. Their diagnoses included schizophrenia, schizoaffective disorder, bipolar disorder, and posttraumatic stress disorder. Concurrent antipsychotic medications were received by 39% of the clozapine patients, 24% of the risperidone patients, 47% of the olanzapine patients, and 73% of the quetiapine patients (the difference between risperidone and the other three groups was significant; p<0.05).

Psychiatric admissions were significantly more frequent in the clozapine group (71.1 per 100 patients) than the risperidone group (65.8 in both; p<0.05). Length of hospital stay after psychiatric admissions was shorter in the risperidone group (17.8 days), than the clozapine (40.5 days), olanzapine (20.1 days), or quetiapine groups (51.2 days).

CONCLUSION: Total costs of treatment (antipsychotic drug + concurrent psychotropics + psychiatric admission and visit cost/patient/year) were lower for risperidone ($128,013) than clozapine ($309,665), olanzapine ($134,502), or quetiapine ($233,415). Presented at the International Congress on Schizophrenia Research Biennial Meeting, Santa Fe, NM, April 17-21, 1999.

149E. Atypical antipsychotics: differences in length of stay, length of remission and total daily cost. Stephen R. Saklad, Pharm.D., Larry Ereshety, Pharm.D., Denise J. Pabco, Pharm.D., Daniel J. Still, Pharm.D., June E. Vertrees, Pharm.D.; University of Texas, Austin, TX; State Hospital of San Antonio, San Antonio, TX.

PURPOSE: Outcomes and effectiveness of atypical antipsychotics were analyzed using data combined in a pharmacy distribution system and an administrative database.

METHODS: Data (1994-1998) from the San Antonio State Hospital (SASH) pharmacy and the Texas Department of Mental Health and Mental Retardation were analyzed. Inclusion criteria: a single atypical antipsychotic prescribed on discharge from SASH and the patient was subsequently readmitted.

RESULTS: Of the 377 patients (546 admissions) 59% were male; 48% were Hispanic, 40% Caucasian, 11% African American, and 1% other. Age at discharge was 35 ± 12 years. Primary DSM diagnoses were schizophrenia (109 patients), and schizoaffective disorder (32%). Mean period between discharge and readmission was 226 days on risperidone (n=303), 205 days on clozapine (n=69); 136 days on olanzapine (n=178); and 36 days on quetiapine (n=7). Olanzapine vs risperidone was significant with p<0.001. Mean length of stay was 442 days on clozapine; 110 days on risperidone; 101 days on olanzapine; and 71 days on quetiapine (clozapine vs olanzapine p<0.001; clozapine vs risperidone p<0.0001). Mean total daily cost of drug therapy was $11.88 for clozapine; $9.94 for olanzapine; $7.67 for quetiapine; and $6.08 for risperidone (clozapine vs risperidone p<0.0001; clozapine vs olanzapine p<0.0001).

CONCLUSIONS: Length of stay was greater for patients discharged on clozapine than either olanzapine or risperidone. Length of remission was greater for patients discharged on risperidone than olanzapine. Total daily cost of pharmacotherapy was less for patients discharged on risperidone than clozapine or olanzapine.


PURPOSE: Inpatient treatment of intra-abdominal infections (IAI) has important cost components including length of stay (LOS), costs of IV drugs, costs of adverse events, and post discharge outcomes.

METHODS: Hospital time-to-discharge (H-TTD) was assessed for 258 IAI patients who received piperacillin/tazobactam (pip/tazo 4 g/500 mg) or imipenem/cilastatin (imp/cil 1 g/1 q) q6h in a randomized, double-blind, efficacy/safety study in 422 patients. Severity was evaluated by using the APACHE II scores and accounting for censored hospital days due to in-patient death, a Cox proportional hazards analysis was used to estimate H-TTD.

RESULTS: Unadjusted baseline APACHE II scores were higher in the pip/tazo group than in the imp/cil group, especially among the intent-to-treat population (ANOVA, p<0.02). The pip/tazo group had a 23% lower instantaneous rate of hospital discharge (IRHD), and a proportionally greater extended median H-TTD, compared with the imp/cil group (p<0.04). After adjusting for severity by using APACHE II scores, treatment-related differences in IRHD were not statistically significant (p=0.13) and post discharge outcomes (e.g., need for oral antibiotics) were similar. Treatment of the primary infection required an average of 7.6 days on pip/tazo vs 7.1 days for imp/cil. Imputing costs for study drugs (imp/cil $169.89 vs pip/tazo $64.26) translated into a saving of $718 per course of therapy.

CONCLUSIONS: Treatment with pip/tazo is equivalent to that of imp/cil in duration and efficacy and is expected to save costs.


PURPOSE: To compare the cost-effectiveness of sevelamer hydrochloride to calcitriol for reducing LDL-C cholesterol in patients with hyperphosphatemia.

METHODS: A cost-effectiveness model was developed from the perspective of the consumer. We compared the total yearly costs of sevelamer 2 capsules TID AC to calcium carbonate 1 g TID AC + atorvastatin 10 mg QD for reduction of LDL-C. The decision tree used data obtained from published and site-specific sources regarding percentage estimates of safety and efficacy (goal 30% LDL-C reduction) and costs and prices associated with both regimens. The target population included CRF patients without HD but with 2 CHD risk factors and LDL-C between 160-190 mg/dl and stable phosphorus concentrations < 7.5 mg/dl.

Sevelamer and calcium carbonate were assumed to be equivalent in their phosphorus-lowering ability. Outcome measures included total cost, and cost per goal LDL-C achieved.

RESULTS: The combination of calcium carbonate 1 g TID AC + atorvastatin 10 mg QD was more cost-effective than sevelamer 2 capsules TID AC. Total yearly costs were $1486 and $1852 for calcium carbonate + atorvastatin and sevelamer, respectively, per patient treated. The cost-effectiveness ratio (cost/patient achieving goal LDL-C) was $1736 and $3679 for calcium + atorvastatin and sevelamer, respectively. One way sensitivity analysis validated our cost-effectiveness model.

CONCLUSIONS: This analysis suggests calcium carbonate 1 g TID AC + atorvastatin 10 mg QD is more cost-effective than sevelamer 2 capsules TID AC for the treatment of hyperlipidemia in CRF patients with hyperphosphatemia.

152. Cost-minimization analysis of phenytoin and fosphenytoin in the emergency department. Daniel R. Touchette, Pharm.D., Denise H. Rhoney, Pharm.D.; Wayne State University; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: To determine the value of fosphenytoin compared with phenytoin in the treatment of post-seizure patients in the emergency department (ED).

METHODS: We developed a simple decision analytic model representing the variable costs of treating post-seizure patients in the ED. A cost-minimization analysis comparing phenytoin and fosphenytoin was performed from a hospital perspective. Adverse event rates and resource utilization for events were estimated from a comparative clinical trial involving 256 patients in our institution (base case). Charts were abstracted to identify delayed complications such as purple glove syndrome (PGS). Sensitivity analyses and a scenario analysis were performed to determine the robustness of the model.

RESULTS: In our base case, phenytoin was the preferred option, with an expected total treatment cost of $5.39 compared with $110.14 for fosphenytoin. Although delayed complications were not observed in any of our patients, sensitivity analyses demonstrated that the incidence and cost of treating PGS could univariately affect the decision. A two-way sensitivity analysis indicates that at an incidence of 1%, the average cost of treating PGS must be greater than $10,000 to make fosphenytoin a preferred option. A Monte Carlo simulation showed phenytoin was the preferred option 97.3% of the time. The scenario analysis also favored phenytoin ($32.38) to fosphenytoin ($110.86).

CONCLUSIONS: When the variable costs of care are used to calculate the value of phenytoin compared with fosphenytoin in the ED, phenytoin is the preferred option. The decision to use phenytoin was very robust and changed only when both the incidence and cost of PGS was high.

153. Comparison of erythromycin, clarithromycin, amoxicillin/clavulanate, and cefuroxime axetil for treatment of outpatient community-acquired
RESULTS: Six medications, atorvastatin, simvastatin, fluvastatin, lovastatin, gemfibrozil, and pravastatin, were used by 98.1% of the patients. 280 (10%) of patients had no CLM claim during the study period. Patients receiving more than one of the study drugs were excluded. Survival analysis was used to examine the probability of discontinuing therapy was defined as drug discontinuation was defined as receipt of no drug claim(s) for a CLM during the study period. Sensitivity analysis using 10,000 Monte Carlo simulations demonstrated that the median (SD) and mean (95% CI) of duration of therapy without a prescription claim for taking a CLM was 7.4 ± 0.6 months. The probability of receiving a CLM was 2.1 ± 0.4% of the total body activity. Renal clearance of 99mTc-P280 was defined as 1.0 ± 1.3 ml/min (74 ± 21% of total body clearance). The distribution of a CLM was defined as having an extrapolated clearance of 7.0 ± 6.7 ml/min (74% ± 21% of total body clearance).

CONCLUSIONS: Due to the high cost of hospitalization and low probability of death due to any cause, the mean (SD) and median (95% CI) of duration of therapy without a prescription claim for taking a CLM was 7.4 ± 0.6 months. The probability of receiving a CLM was 2.1 ± 0.4% of the total body activity. Renal clearance of 99mTc-P280 was defined as 1.0 ± 1.3 ml/min (74 ± 21% of total body clearance). The distribution of a CLM was defined as having an extrapolated clearance of 7.0 ± 6.7 ml/min (74% ± 21% of total body clearance).

Pharmacokinetics/Drug Metabolism

155. An open label study evaluating the pharmacokinetics of 99m technetium P280 in patients at risk for venous thrombosis. William B. Webster, Pharm.D., Tina Vo, Pharm.D., Andrew F. Nasser, B.S., Steven J. Harwood, M.D., Ph.D., Sam Hakki, M.D., Robert G. Carroll, M.D., Michele Montemayor, B.S., John Camblin, M.D., Tatjana Webster, M.D., Barry Pines, VA Medical Center, Bay Pines, FL; University of Florida, Gainesville, FL; Nova Southeastern University, Ft. Lauderdale, FL; Mercer University, Atlanta, GA; University of South Florida.


METHODS: Patients were assessed for possible influence of patient demographics on the pharmacokinetics of a new antibody-chemotherapeutic agent for relapsed acute myelogenous leukemia (AML) who received therapy. After adjusting for these differences, patients prescribed amiodarone were significantly less likely (p<0.01) to discontinue treatment (odds ratio 0.65, 95% CI: 0.50 to 0.85), and had more covered days of medication over one year (63% versus 55% for felodipine; p<0.01). More patients in the amiodarone group (77% versus 66% for felodipine) were started at a lower dose (2.5 or 5.0 mg daily). The final adjusted daily dose (mean ± SD) was also lower (p<0.05) for amiodarone (6.6 ± 3.7 mg) than for felodipine (7.3 ± 4.1 mg).

CONCLUSIONS: In routine clinical practice, comorbidities, medication dosing, and treatment adherence may differ among patients who are prescribed drugs that are viewed as being pharmacologically similar. These factors may be important for therapeutic decision making.


METHODS: CMA-676 is a novel chemotherapeutic agent that consists of a human engineered anti-CD33 antibody (hP67.6) linked to a cytotoxic agent, N-acetyl-gamma calicheamicin DMH, with a bifunctional AcBut linker. The pharmacokinetics of CMA-676 was determined in patients with relapsed acute myelogenous leukemia (AML) who received toxic as the result of infusion have been determined. Plasma samples were assayed for hP67.6 and calicheamicin derivates (total and unconjugated) by enzyme-linked
immunosorbent assays and pharmacokinetic parameters were determined by noncomparitional methods. Comparisons between groups were made by analysis of variance.

RESULTS: The mean (± SD) PH76.6 pharmacokinetic parameters for the first dose period are:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (± SD)</th>
<th>Median (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>27.8 ± 4.5</td>
<td>26.4 ± 4.2</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>AUC (mg·h/L)</td>
<td>94.3 ± 18.7</td>
<td>92.7 ± 18.0</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>1.2 ± 0.2</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.2 ± 0.04</td>
<td>0.2 ± 0.03</td>
</tr>
</tbody>
</table>

There was no difference observed when comparing men to women, nor when comparing patients greater than or equal to 60 years of age to those less than 60 years of age (p>0.05). The concentration-time profiles of calicheamicin were similar to PH76.6, with no relationship observed between pharmacokinetics and demographics.

CONCLUSION: No influence due to gender, age, or weight was observed in the CMA-476 pharmacokinetic parameters of 58 patients with relapsed AML.

158. Evaluation of vancomycin dosing and monitoring strategies in hematologyn/ oncology patients. Sheila A. Salamunovich, Pharm.D., Paul M. Beringer, Pharm.D., Alfred Chin, Pharm.D.; University of Southern California, Los Angeles, CA.

PURPOSE: To determine the accuracy and precision of a published pharmacokinetic model in predicting serum vancomycin concentrations (SVC), and to evaluate the applicability of a recently published vancomycin dosing nomogram in hematologyn/oncology patients.

METHODS: Forty-eight patients who met the inclusion criteria were identified by a retrospective analysis of concurrently gathered vancomycin data. First, a priori predictions of all SVC were performed using a published two-compartment pharmacokinetic model. Second, Bayesian analysis was used to predict future SVC based on a) the first set of measured peak and trough concentrations, and b) the first measured trough concentrations. Third, future SVC were predicted using a published vancomycin nomogram.

RESULTS: A significant correlation (0.81) was observed between predicted and measured SVC. There was no significant difference in predicted future SVC among the various monitoring strategies. Target trough concentrations were achieved in 68% of the patients utilizing the nomogram.

159. One-day aminoglycoside monitoring: sampling considerations for an extended distribution phase. Heath R. Jennings, Pharm.D., Elizabeth A. Coy, Pharm.D., Michelle L. Keaner, M.D., George A. Davis, Pharm.D.; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: A recent study in healthy volunteers demonstrated a prolonged distribution phase following the administration of one-day aminoglycosides (ODA). This has led to questioning of the accuracy of conventional ODA sampling strategies that assume complete drug distribution in 60 minutes. The purpose of this study is to evaluate a conventional two-concentration sampling strategy by determining the difference in pharmacokinetic parameters when considering prolonged distribution.

METHODS: In this prospective study of 20 surgery patients, gentamicin or tobramycin (7 mg/kg) was infused over 30 minutes. Peak (Cpeak) and two random concentrations (C30 and C60) were obtained 0.5, 3.5, and 9.5 hours post-infusion, respectively. Pharmacokinetic parameters (PK) and an estimated 24-hour trough (C24h) were calculated using two concentration strategies: a conventional strategy using Cpeak and C30, and a study strategy using C30 and C60. An estimated peak (Cpeak) was calculated using the study strategy.

RESULTS: Dose = 70 ± 6 mg/kg; PK parameters (conventional and study, respectively): Cpeak = 22.5 ± 6.1 mg/L and C30 = 14.3 ± 3.2 mg/L (p>0.001); C30 = 0.24 ± 0.46 mg/L and C60 = 0.47 ± 0.92 mg/L (p>0.001); V1 = 0.27 ± 0.08 L/kg and V2 = 0.44 ± 0.11 L/kg (p>0.001); k = 0.26 ± 0.09 h⁻¹ and k2 = 0.20 ± 0.08 h⁻¹ (p>0.001).

CONCLUSION: PK parameters based upon conventional ODA sampling strategies may not be optimal since C24h appears to be drawn during the distribution phase. Clinical significance includes an overestimation of Cpeak/MIC, and an underestimation of C24h. Specifically, 14 patients (70%) would have received incorrect or unnecessary dosage adjustments and 3 patients (15%) would have been inappropriately re-dosed with a trough concentration >2 mg/L. If conventional sampling strategies were utilized, considering these results, a revised two-concentration sampling strategy may be warranted.

160. Morphine pharmacokinetics in African-American males with and without sickle cell anemia. Aaron H. Burststein, Pharm.D., Jason A. Gross, Pharm.D., Michael Williams, B.S.N.; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: To evaluate single-dose morphine pharmacokinetics (PK) following intravenous (IV) administration in sickle cell anemia patients (SCA) not in vaso-occlusive crisis and race-matched normal volunteers (N).

METHODS: Morphine (10 mg) was administered as an IV injection over 2 minutes. Blood samples for determination of morphine plasma concentrations were collected at baseline and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 7, and 8 hours following initiation of dosing. Samples were analyzed by HPLC (LLOQ 3 ng/ml).

RESULTS: Data were fit (WinNonlin v1.5) by a linear, open, 2-compartment model. Noncompartmental analysis was performed to determine area under the curve to infinity (AUC0-∞). Maximal concentration (Cmax), and half-life (t1/2) were determined by visual inspection of data. Comparison of PK between SCA and N was by Wilcoxon signed rank test.

CONCLUSIONS: No differences were found in PK parameters between SCA and N.

161E. St. John's wort: evaluation of effect on CYP3A4 and CYP2D6 activity. E. St. John's wort: evaluation of effect on CYP3A4 and CYP2D6 activity. E. St. John's wort: evaluation of effect on CYP3A4 and CYP2D6 activity. E. St. John's wort: evaluation of effect on CYP3A4 and CYP2D6 activity. E. St. John's wort: evaluation of effect on CYP3A4 and CYP2D6 activity.

PURPOSE: To evaluate the effect of reagent grade St. John's wort on CYP3A4 and CYP2D6 activity.

METHODS: Normal healthy volunteers, 18-45 years old, medication free for at least 2 weeks, ingested a 300 mg tablet of 0.3% hypericin standardized reagent grade St. John's wort three times a day for 14 days. Baseline (day 0) and post-treatment (day 14) CYP3A4 and CYP2D6 activities were evaluated using urine 6β-hydroxycortisol/cortisol and dextromethorphan/dextrorphan (DM/DS) ratios, respectively. At baseline and post-treatment 30 mg of dextromethorphan was ingested followed by urine collection for 24 hours. Urine specimens were analyzed by HPLC. Baseline and day 14 ratios were compared using the paired Student's t-test with statistical significance declared at p<0.05.

RESULTS: Thirteen subjects (4 males, 9 females) with a mean (SD) age of 30 (7.5) years completed the study. The mean (SD) urine 6β-hydroxycortisol/cortisol ratio significantly increased from a baseline value of 7.1 (4.5) to 13 (4.9) after treatment (p=0.003), with a mean (SD) increase of 114% (115%). The mean (SD) urine DM/DS ratios at baseline and post-treatment were 0.0063 (0.0066) and 0.0070 (0.0090), with a mean (SD) increase of 17% (p=0.675).

CONCLUSIONS: Treatment with reagent grade St. John's wort for 14 days resulted in a 114% increase in urine 6β-hydroxycortisol/cortisol ratios implicating St. John's wort as an inducer of CYP3A4. No significant effect was seen on the CYP2D6 surrogate marker dextromethorphan. The potential for drug-drug interactions involving the CYP3A4 metabolic pathway should be considered.


PURPOSE: To assess the effects of mexiteline and mexiteline in healthy volunteers. Mexiteline (10 mg) was administered as a single oral dose to 8 volunteers who were then randomized to receive celecoxib (200 mg BID), alone or in combination with mexiteline (5 mg BID). Blood and urine specimens were collected for 24 hours and the alternative regimen on days 8-14. Blood and urine specimens were collected for 24 hours and the alternative regimen on days 8-14.

RESULTS: Twenty-six men and 6 women (17 Caucasians, 10 African-Americans, 4 Hispanics and 1 other) with a mean age of 35.5 years completed...
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163. Effects of a high fat meal on the absorption of M100907 in healthy subjects. Dan C. Dimmitt, B.S., Michael B. Doherty, Pharm.D., Ruth E. Emptage, John Shelton, Ph.D., Doris Robbins-Weilert, Formulations. With the oral liquid, the T max increased about 1.2 hours with bioavailability of plasma M100907 compared to the fasted treatment.

METHODS: In three studies, 20 mg single doses of M100907 prototype tablets, commercial tablets, and a commercial oral liquid formulation. Studied subjects) were administered in a crossover design. Drug administrations were given following both high-fat breakfast and fasted treatments. Blood samples were collected to 60 hours post dose and quantitated for plasma M100907.

Bioavailability comparisons within each formulation were made between the fed and fasted treatments to assess the food effect.

RESULTS: With all formulations, the high-fat breakfast increased the bioavailability of plasma M100907 compared to the fasted treatment. Increases in mean ∞Cauc ranged from 39% for the prototype tablet to 25% for the oral liquid. Increases in mean C max were 33% and 42% for the commercial tablet and prototype tablet, respectively, with the oral liquid showing no increase in C max with the fed treatment. Terminal t1/2 did not change in all comparisons and the T max was unchanged in both tablet formulations. With the oral liquid, the T max increased about 1.2 hours with fed treatment compared to fasted treatment.

CONCLUSIONS: While increases in bioavailability of up to 39% were observed with M100907 formulations when given with a meal, these changes would not alter the therapeutic or safety profile of the drug because of the tolerability seen in healthy volunteers.

Pharmacy Practice

164. Assessment of asthma outcomes in a pharmacotherapy clinic. Bryan F. Yeager, Pharm.D., BCPS; University of Kentucky, Lexington, KY.

PURPOSE: To evaluate the clinical outcomes of a pharmacist-managed clinic compared to traditional care for asthmatic patients seen in a university-based family medical center.

METHODS: Sixty-five patients with a diagnosis of asthma were screened by medical record review and phone interview to determine eligibility. Patients determined to be high-risk for asthma complications if they had: 1) history of medication nonadherence, 2) average peak expiratory flow rate < 80% of personal best, 3) asthma-related emergency room visit in the last 12 months, or 4) ≥ 2 drug-active beta-agonist use > 2 times per week. High-risk asthmatic patients were enrolled into a pharmacotherapy clinic (PTC) for collaborative drug therapy management and patient education. Individuals were seen in clinic every 2 to 4 weeks. Clinical outcomes, medication adherence and emergency room visits were measured 3 months before and after PTC enrollment.

RESULTS: Mean peak expiratory flow rates were higher after PTC enrollment compared to traditional care (93% vs 72% of personal best, p<0.001). There was a favorable trend decreased towards decreased beta-agonist use per visit (25 vs 2, p=0.08), long-term control medication adherence (54.4% vs 37.5%, p=0.10) and emergency room visits (3 vs 1, p=0.05) for patients before and after PTC enrollment.

CONCLUSIONS: Asthma control is improved for high-risk patients referred to and seen routinely in a pharmacist-managed clinic. This improved control may be due to better adherence with long-term control medications, adjustment or initiation of long-term control medication, more frequent home monitoring and educational efforts.

165. Evaluating the impact of providing smoking cessation services to an indigent population. Mark E. Rittman, Pharm.D., Ruth E. Emptage, Pharm.D., Martin R. Giannamore, Pharm.D., Craig A. Pedersen, Ph.D.; The Ohio State University, Columbus, OH.

PURPOSE: Smoking cessation programs provided to the general population report cessation rates of 25.5%. This study evaluated smoking cessation rates and abstinence barriers of indigent patients enrolled in a pharmacist-managed smoking cessation program at a primary care setting. Patients' perceived change in health status and overall satisfaction with the program were also evaluated.

METHODS: Patients that attempted to quit smoking as part of a smoking cessation program were evaluated. Data collection occurred in three phases for each patient: retrospective chart review and phone call survey 6 months after enrolling in the program.

RESULTS: Thirty-three patients enrolled in the program qualified for evaluation. Six month cessation rates were 27.3% (95%). Twenty-four of 33 (73%) of patients completed the survey, eight months after quitting smoking (32%). Unsuccessful patients identified stress as the main reason for relapse (7/16, 43.8%). Patients viewed personal visits with pharmacists as the greatest strength of the program (11/24, 45.8%), while difficulty obtaining medications was identified as the greatest weakness (2/16, 12.5%). Patients who quit smoking viewed their health as better (p<0.02) and were more satisfied with the program (p=0.02) than those who did not quit smoking. Regardless of smoking status, patients were satisfied with the program: 8/16 (50%) quitters and 14/16 (87%) non-quitters.

CONCLUSIONS: Comparable cessation rates between an indigent and general population demonstrate the value of providing services to an underserved population. Improving stress management strategies and medication accessibility may further enhance cessation rates and the quality of the program.

166. Effect of pharmacist initiated home blood pressure monitoring on hypertension. Brenda M. Mehos, Pharm.D. (Joseph J. Saseen, Pharm.D., Eric J. MacLaughlin, Pharm.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: This study evaluated the impact of pharmacist initiated home blood pressure (BP) monitoring on BP control, medication compliance, and quality-of-life (QOL).

METHODS: Thirty-six subjects met inclusion criteria in this six-month prospective, randomized, controlled study. All patients received initial counseling on drug therapy and lifestyle modification. Intervention subjects (n=18) received home BP monitors, a diary, and instructions to measure BP twice daily. Clinical pharmacists in a family medicine clinic evaluated subjects' home measurements. Primary care physicians were contacted with recommendations if mean BP values were ≥ 140/90 mm Hg. Control patients did not receive home monitors or pharmacist intervention. Office BP measurements and QOL surveys (SF-36) were obtained at baseline and after 6-months.

RESULTS: Systolic BP (SBP) and diastolic BP (DBP) were significantly reduced from baseline to intervention subjects (mean absolute SBP/DBP reductions 17.0/10.5; both p<0.001) but not in control subjects (mean absolute SBP/DBP reductions 7.0/3.8; p=0.12/p=0.09). Mean percent decreases in SBP/DBP from baseline were greater in intervention versus control subjects (10.4%/11.0% versus 4.3%/3.6%; p=0.06/p=0.02). More intervention subjects (8 of 18) had controlled BP (<140/90) at 6 months compared to controls (4 of 18). During the 6-month study period, 83.3% (15 of 18) of intervention subjects had medication changes versus only 33% (6 of 18) in the controls (p=0.01). Medication compliance and QOL were not significantly affected.

CONCLUSIONS: Our data suggests that the combination of pharmacy intervention with home monitoring can improve BP control in uncontrolled hypertensive patients. This may be related to increased modifications of drug regimens. Presented at the 100th Annual Meeting of the American Association of Colleges of Pharmacy, Boston, MA, July 3-7, 1999.

167. Interventions performed by clinical pharmacists in high-risk ambulatory veterans: the IMPROVE trial. Samuel L. Ellis, Pharm.D., Daniel C. Malone, Ph.D., Barry L. Carter, Pharm.D., University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: This randomized, prospective study evaluated patient care interventions provided by ambulatory care clinical pharmacists during the Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers (IMPROVE) study.

METHODS: A total of 523 patients were randomized into the intervention arm of this multi-centered study in nine Veteran Affairs medical centers. Patients were selected for this study if they were considered to be at high risk for medication-related problems. Pharmacists were asked to document, on a standard form, length of visit, method of contact, medical problems addressed and drug-related problems addressed and resolved during each intervention.

RESULTS: Seventy-eight ambulatory care clinical pharmacists documented a total of 1855 interventions, an average of 3.54 ± 2.31 per patient, over a 12-month period. The length of visits was ≥ 15 minutes for 73% of interventions. In-person interventions accounted for 1421 visits (76.6%) with the remainder being telephone contacts. During each intervention the average number of drug-related problems addressed and resolved was 3.60 ± 1.4 and 1.11 ± 0.97, respectively. More drug-related problems were addressed and resolved when visits were ≥ 15 minutes (p=0.001) and when the method of pharmacist-patient contact was in person (p<0.001).

CONCLUSIONS: Ambulatory care clinical pharmacists addressed and resolved more problems when seeing patients in person as compared to using telephone. This may provide valuable information to clinical pharmacists.
developing pharmacy-managed clinics for patients at high risk for medication-related problems.

**Psychiatry**


**PURPOSE:** Olanzapine plasma concentrations > 9.3 ng/ml (24 hours post-dose) have been identified as a predictor of clinical response in acutely ill schizophrenic patients. We report a receiver operator characteristic (ROC) curve analysis of 12-hour olanzapine concentrations and therapeutic response from the North American Double-Blind Olanzapine Trial.

**METHODS:** Patients meeting DSM-III-R criteria for schizophrenia were randomized to receive olanzapine, haloperidol or placebo. After a 4-7 day placebo lead-in, patients randomized to olanzapine received daily doses ranging from 2.5 to 17.5 mg/day for up to six weeks. Olanzapine samples were obtained between 10 and 16 hours (11.7 ± 1.7 hr) post-dose.

Therapeutic response data and olanzapine concentrations used for analysis were derived from the endpoint visit for each patient if the patient had been on a fixed olanzapine dose for at least the last two weeks of the study. Plasma concentrations from previous visits were used if endpoint concentrations were invalid. Response was defined as ≥ 20% reduction in Brief Psychiatric Rating Scale (BPRS) and a clinical global impression severity score of ≤ 3 or a final BPRS of ≤ 35.

**RESULTS:** The final ROC analysis included data from 84 patients. Fifty-two percent of patients with 12-hour olanzapine concentrations ≥ 22.3 ng/ml responded, whereas only 25% of patients < 22.3 ng/ml responded. Furthermore, this threshold was a predictor of response in the Scale for the Assessment of Negative Symptoms.

**CONCLUSIONS:** A 12-hour olanzapine plasma concentration of ≥ 22.3 ng/ml was a predictor of therapeutic response in acutely ill schizophrenic patients.

172. Prolactin elevations in patients treated with olanzapine. Daniel R. Wilson, M.D., Leo D’Souza, M.D., Henry Nasarallah, M.D., Mark Newman, M.D.; The Lewis Center, Cincinnati, OH; University of Mississippi Medical Center, Jackson, MS.

**PURPOSE:** With the advent of novel antipsychotic compounds relatively free of extrapyramidal symptoms, increased interest is now directed to other side effects and their clinical relevance. Systematic studies of such side effects are limited.

**METHODS:** In a 6-week open-label study, the authors evaluated the prolactin response in patients receiving a fixed titration schedule of olanzapine. All patients were enrolled in an academically affiliated state hospital adult inpatient unit and all met DSM-IV criteria for schizophrenia. The dose of 30 mg/day of olanzapine was achieved in 2 weeks. Serial serum assays were obtained from fasting samples drawn consistently to control for diurnal fluctuations and possible postprandial effects.

**RESULTS:** Results of preliminary data analysis in the first 10 patients revealed acute and marked prolactin elevations associated with olanzapine in 4 patients, including dramatic elevation in 1 neuroleptic-naïve patient studied. The study is being extended to determine whether these findings are replicated in a larger study population and sustained beyond 6 weeks.

173. Correlation between total cholesterol and response in clozapine-treated patients. Charles F. Calley, Pharm.D., Robert L. Dufrene, Ph.D.; University of Connecticut, Storrs, CT; Institute of Living, Hartford, CT; University of Rhode Island, Kingston, RI; VA Medical Center, Providence, RI.

**PURPOSE:** This study was performed to evaluate the association between total cholesterol and brief psychiatric rating scale (BPRS) score changes in patients with refractory schizophrenia/schizoaffective disorder who were treated with clozapine.

**METHODS:** Medical records of 25 clozapine-treated patients (16M/9F) diagnosed with refractory schizophrenia (n=20) and schizoaffective disorder (n=4) were reviewed retrospectively. Patient demographics, diagnosis, previous antipsychotic treatment, concurrent psychotropic treatment, tardive dyskinesia severity, weight, total cholesterol, serum triglyceride and BPRS scores were documented.

**RESULTS:** Regression analysis indicated that baseline total cholesterol was a significant predictor of changes in total BPRS scores (Pearson r=0.601, p<0.01), thinking disturbance (Pearson r=0.58, p=0.018), depression (Pearson r=0.48, p=0.029), paranoid disturbance (Pearson r=0.558, r²=0.311, p=0.007) sub-scale scores; mean scores were reduced by
approximately 30%. No association was found between baseline total cholesterol and changes in the anxious depression or withdrawal retardation sub-scale scores. Changes in total cholesterol were also not associated with any BPRS score changes. There was no association found between changes in BPRS scores and any of the remaining variables including age, gender, concurrent psychotropic use or weight.

CONCLUSIONS: Higher total cholesterol at treatment onset with clozapine predicted reductions in BPRS total and positive symptom sub-scale scores. Our results suggest that total cholesterol predicts positive symptom response to clozapine in subjects with refractory schizophrenia/schizoaffective disorder.

174E. Association between cytochrome P4502D6 genotype, neuroleptic exposure, and/or noninflammatory treatment scale score. Vicki L. Ellingrod, Pharm.D., BCPP; Susan K. Schultz, M.D., Stephen Arndt, Ph.D.; Paul J. Perry, Ph.D., BCPP; Nancy C. Andreasen, M.D., Ph.D., Tim L. Holman, M.A., Frank Fleming, B.S.N.; University of Iowa, Iowa City, IA.

The metabolism of many antipsychotics cosegregates with the metabolic activity of the polymorphic cytochrome P4502D6 (CYP2D6). Approximately 5-10% of Caucasians show impaired metabolism due to lack of this enzyme. By phenotyping patients for 2D6, we are unable to determine those homozygous for 2D6 (Wt/Wt) and those with a mutation (Wt/Tm). The number of Wt alleles is associated with the metabolic activity of CYP2D6. Genotype is the independent variable.

PURPOSE: To determine if an association between CYP2D6 genotype, neuroleptic exposure, and AIMS score exists.

METHODS: Patients with schizoaffective DMS-III-R were genotyped for CYP2D6*1, *2, and *4 alleles by using nested polymerase chain reaction. Full psychiatric and medication history and evaluations were recorded. Neuroleptic exposure was converted into dose years (chlorpromazine equivalents x years used). A linear model was run with AIMS scores as the dependent variable. Genotype, gender, neuroleptic exposure, and interactions were independent variables.

RESULTS: A total of 31 patients were included. Twenty were Wt/Wt and 11 were Wt/Tm. No poor metabolizers were found. Mean neuroleptic dose years between the two groups were different (Wt/Wt 142.86 ± 74.7 vs Wt/Tm 72.79 ± 60.27; p<0.0125). The interaction of neuroleptic*genotype was the only significant variable (p<0.0055).

CONCLUSION: This association showed that those with the Wt/Tm genotype had a higher association with higher AIMS scores (slope = 0.044) than those with Wt/Wt (slope = 0.001). These results suggest that patients with a mutated CYP2D6 allele are at a higher risk for developing abnormal movements due to neuroleptic use. Published in Schizophr Res 1999;36(1-3):90.


PURPOSE: This retrospective study compares titration rates for patients starting a course of therapy on either olanzapine or risperidone to assess prescribing differences.

METHODS: Patients who were dispensed olanzapine (n=3544) or risperidone (n=23,302) as their first antipsychotic between October 1 and December 31, 1996 were selected from a large U.S. claims database. All antipsychotic prescriptions for one year preceding and following each patient’s first antipsychotic prescription were used to identify initiators (patients with no prior antipsychotic use: olanzapine, n=283; risperidone, n=386) and to calculate titration rates and the time to the first titration. Rates were calculated for all patients and for those aged 18 to 64 with and without accounting for duration of therapy.

RESULTS: Regardless of age and whether duration was taken into account, fewer olanzapine (36.0%, all ages; 37.2% aged 18 to 64) than risperidone (42.6%; 39.3%) initiators were titrated. Differences were significant for all age groups (p<0.05). Similar differences were generally observed for comparisons accounting for duration of pharmacotherapy. The number of days from the first titration occurred later in the course of treatment for olanzapine (86.7; 89.7 days from date of first prescription) than for risperidone (82.2; 83.2 days).

CONCLUSIONS: Patients initiating a treatment episode on olanzapine were less likely to be titrated and were titrated later in the course of therapy than those on risperidone. These results may indicate tolerability, effectiveness, and/or physician practice differences, which should be explored for potential treatment implications.


Combined pharmacotherapy is used increasingly to address treatment resistance, comorbidity and attenuate the adverse effects of medications. Tricyclic antidepressants (TCAs), desipramine (DMI) and others are combined with clonidine or guanfacine to treat complex cases of ADHD with comorbid tic, behavioral or anxiety disorders not responsive to TCAs alone, or to alleviate symptoms of ADHD-associated sleep disturbances in children on TCAs. However, drug-drug interactions may occur between DMI and other medications resulting in decreased DMI clearance and increased DMI toxicity. Thus, it is important to examine if a2-adrenergic agonists on the pharmacokinetics of DMI in children and adolescents to assure the safety of combined pharmacotherapy.

PURPOSE: To examine the influence of clonidine and guanfacine on the pharmacokinetics of DMI using routinely monitored DMI serum concentrations in children and adolescents receiving DMI alone or in combination with a2-adrenergic agonists clonidine or guanfacine.

METHODS: DMI pharmacokinetic parameters were calculated for a total of 157 youth (between 6 and 17 years, 133 males, 24 females) from 441 weight and dose-normalized serum concentrations. Subjects received either DMI (368 serum concentrations, 131 subjects) or DMI + a2-agonist (73 serum concentrations, 26 subjects).

RESULTS: DMI pharmacokinetic parameters, mean weight corrected dose (DMI, DMI + a2-agonist) (slope = 0.171 ± 0.062; p<0.05), were the same between groups. Differences were significant for all other parameters.

CONCLUSION: Due to the significant differences found in DMI pharmacokinetic parameters between the two groups were different (Wt/Wt 142.86 ± 74.7 vs Wt/Tm 72.79 ± 60.27; p<0.0125). The interaction of neuroleptic*genotype was the only significant variable (p<0.0055).

However, the influence of gender on the drug-drug interaction should be examined further in a larger population. Presented at the 39th Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, FL, June 1-4, 1999.

176EA. Pharmacotherapy of attention deficit hyperactivity disorder in psychically referred girls. Louise Glassner Cohen, Pharm.D., Joseph Biederman, M.D., Susan Gilson, Pharm.D., Sabrina Whitl, Pharm.D., Jean Frazier, M.D., Janet Woźniak, M.D., Timothy E. Wiliens, M.D., Thomas Spencer, M.D., Erick Mick, Sc.D.; Massachusetts General Hospital; Harvard Medical School, Boston, MA.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is the most widely diagnosed and researched neuropsychiatric disorder in children and adolescents. Despite the large number of published trials, there is limited research on the pharmacologic, psychosocial and educational interventions in children with ADHD, there are no data to describe the treatment of ADHD in girls. Recent research suggest that gender-related differences in the neuropsychological function in children with ADHD exist. These differences in function, coupled with developmental and gender-related differences in the pharmacokinetics of medications, may significantly influence the pharmacodynamics of medications in girls with ADHD and ultimately influence patient outcome.

PURPOSE: To describe the pharmacotherapy of ADHD in psychically referred girls.

METHODS: Data from a total of 41 girls (33 children and 8 adolescents) referred to the Pediatric Psychopharmacology Unit between 1992 and 1996 for treatment by a board-certified child psychiatrist were retrospectively examined further in a larger population.

RESULTS: The subjects were referred to the pediatric psychopharmacology unit for treatment of ADHD and comorbid disorders at a mean age of (mean ± SD) 9.7 ± 3.2 years. In addition to ADHD, 14 had major depressive disorder (34%), 17 had ODD (41%), S had bipolar II disorder (12%), 11 had one or more anxiety disorders (30%). Of these, 28 (65%) had received previous drug therapy; 20 (48%) had received therapy for ADHD, and of these, 13 (31%) had received stimulants. The average length of treatment captured was 646 ± 502 days, 21 (70%) in 185 days. With the DMI + a2-agonist pharmacotherapy for the treatment of ADHD and comorbid disorders was common. Of the courses of treatment described in the study, 18 (46%) subjects received with only one medication, 27 (65%) received two medications, three medications. Mick, Sc.D., Thomas Spencer, M.D., Erick Mick, Sc.D., Massachusetts General Hospital, Harvard Medical School, Boston, MA.
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PURPOSE: To analyze characteristics of psychotropic drug usage in South Australian extended care facilities. This baseline data will be used to measure the effect of an academic detailing intervention directed at reducing falls in these facilities.

METHODS: Patterns of psychotropic drug prescribing and administration were examined for a cohort of 924 residents of randomly selected South Australian hostels and nursing homes. Data were collected by retrospective review of medication charts over a 14-day period.

RESULTS: The most commonly encountered psychotropic drugs were the benzodiazepines, prescribed for 408 (44%) of patients. Temazepam was the most prescribed psychotropic agent (n=269, 29%), with other commonly prescribed agents being diazepam (n=67, 7.3%) and oxazepam (n=69, 7.4%). The option to administer benzodiazepines on a “when required” basis was specified in less than 50% of cases. Antipsychotic medication was prescribed for 222 subjects (23.9%), with pericyazine the most commonly used agent from this class (n=110, 11.8%). Prophylactic anticholinergic medication was available to less than 1% of subjects. Antidepressants were prescribed for 264 subjects (28.4%), with the most commonly used classes being tricyclic antidepressants (n=46) and serotonin reuptake inhibitors (n=106). In over 50% of cases, tricyclic antidepressants were prescribed at a dose of less than 50 mg. The most commonly prescribed antidepressant agent was sertraline (n=67).

CONCLUSION: Psychotropic drug use was prevalent in this cohort. Several characteristics of drug patterns may contribute to the likelihood of falls, and will be targeted in the intervention phase of the study.

177A. Outpatient SSRI dosing in the VA system. John C. Voris, Pharm.D.; University of South Carolina; Columbia, SC.

PURPOSE: The study was designed to answer the questions: What are the average outpatient doses of fluoxetine, paroxetine, and sertraline? What affects the changes in average daily cost, and is there dose escalation?

METHODS: Data were collected on more than 111,000 outpatient SSRI prescriptions from eight VA hospitals in three adjoining states. Data (average daily cost, dose and number of prescriptions for each drug) were divided into three six-month groups, covering a total of 2.5 years.

RESULTS: The average daily dose for fluoxetine decreased 18% throughout the study (30.9 mg/day to 25.3 mg/day). The cost of the drug only increased approximately 1%. The proportion of the 10 mg capsule increased from 2.8% of the total fluoxetine prescriptions to 6.1%. Sertraline’s average dose increased from 8.4% to 9.3%. The 100 mg tablet was used 75.6% initially, increasing to 80.1%. Paroxetine’s daily dose of 24.2 mg/day increased to 25.1 mg/day (3.7% increase). Daily drug cost remained stable while the use of the 20 mg dose decreased from 96% of all paroxetine prescriptions to 62.1%.

CONCLUSION: Fluoxetine’s dose decreased significantly, sertraline increased. Fluoxetine’s increased cost increase was due to greater use of the 10 mg capsule. Paroxetine’s level cost due to greater use of higher (level priced) strengths. Sertraline’s cost increased due to higher dose and acquisition cost. Sertraline is the most prescribed SSRI.


PURPOSE: A multicenter, randomized, double-blind comparison of risperidone (RIS) and haloperidol (HAL) in stable outpatient schizophrenics and patients with schizoaffective disorder was conducted to compare the time to relapse.

METHODS: Patients continued double-blind treatment until the last patient had completed 1 year. Assessments were made weekly for the first 4 weeks and at 4-week intervals thereafter. Scales used to assess efficacy included the total score on PANSS and all PANSS subscale scores. Safety evaluations included vital signs, physical laboratory tests, and concomitant medication parameters.

RESULTS: Of 365 treated patients in the trial, 41 (23.2%) in the RIS and 65 (34.6%) in the HAL groups relapsed by the end of the first year (p<0.009).

During the entire trial, 45 (25.4%) patients on RIS and 75 (39.9%) patients on HAL relapsed (p<0.002). Patients in the RIS group experienced only a modest degree of weight gain (5.0 pounds at endpoint), a low rate of TD (0.6%), and a low rate of EPS.

CONCLUSIONS: This study provides evidence for the long-term effectiveness of RIS and corroborates earlier pivotal trials in which RIS was found to be significantly superior to HAL against both symptoms of relapse and symptoms of schizophrenia. Previous short-term trials have shown RIS to be statistically superior to HAL in the control of positive and negative symptoms. This trial confirms the superior efficacy of RIS over HAL in long-term treatment. Patients treated with RIS also experienced a desirable safety profile in long-term treatment. Presented at 54th Annual Scientific Convention of the Society of Biological Psychiatry, Washington, DC, May 13, 1999.

Pulmonary

179. The role of nebulized magnesium sulfate in addition to standardized therapy with albuterol in the treatment of acute asthma exacerbations in adults. Olga Bessmertny, Pharm.D., Henry Cohen, M.S., Pharm.D., Ellen Becker, Ph.D., Thomas Johnson, M.S., Darrell Looney, M.D., Jonathan Golden, M.D., Lewis Kohl, D.O., Robert D. DiGregorio, Pharm.D.; Shands Hospital at the University of Florida, Gainesville, FL; Long Island University; Brookdale University Hospital and Medical Center, Brooklyn, NY.

PURPOSE: To compare the efficacy and safety of alternating treatments of nebulized magnesium sulfate (MgSO4) and albuterol to that of albuterol and normal saline in adult patients with mild-to-moderate acute asthma exacerbations.

METHODS: Patients were randomized to receive nebulized MgSO4 (384 mg in 6 ml) or an equal volume of placebo (normal saline) in a double-blind fashion after each dose of nebulized albuterol (2.5 mg/ml) every 20 minutes for the first hour of the study. Spirometry was performed at baseline and every 20 minutes for two hours. Monitoring for safety included vital signs, pulse oximetry, and serum magnesium levels. Improvement in percent-predicted forced expiratory volume in first second (FEV1) was chosen as a primary efficacy endpoint. Secondary efficacy endpoints included improvement in percent-predicted peak expiratory flow rate (PEFR) and rate of hospital discharge.

RESULTS: Seventy-four patients were equally randomized to each of the study groups. There were no statistically significant differences in baseline patient characteristics with exception of age, height, and weight. There were no statistically or clinically significant differences between two study groups in primary or secondary efficacy endpoints. There were no significant differences in vital signs, pulse oximetry or serum magnesium levels at any point during the study. The most common reported adverse events were dizziness, headache, somnolence, bitter taste of the study drug, and burning sensation in the throat.

CONCLUSIONS: The combination of nebulized MgSO4 and albuterol provides no additional benefit over the standardized therapy with albuterol and normal saline in adult patients with mild-to-moderate asthma exacerbations.

Substance Abuse/Toxicology

180. Influence of smoking cessation on dehydroepiandrosterone and DHEA-sulfate concentrations. Eric A. Wright, Pharm.D., Sherril L. Aspillar, Pharm.D., Melissa McNiel, M.D., M. Maggie Folan, B.S.N.; Roslyn A. Stone, Ph.D., Patricia D. Krobott, Ph.D.; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Acute cigarette smoking increases concentrations of adrenocorticotopic hormone (ACTH), which stimulates adrenal secretion of not only cortisol, but also dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S). Epidemiological studies have shown that DHEA-S, the most abundant hormone in the systemic circulation, is higher in habitual smokers than in nonsmokers. There have been no longitudinal studies to date describing DHEA and DHEA-S concentrations during the acute smoking period. This study was designed to determine the effects of smoking cessation on serum concentrations of DHEA and DHEA-S in subjects enrolled in a smoking cessation clinic.

METHODS: We conducted a prospective, longitudinal, naturalistic study at the smoking cessation clinic of the VA Pittsburg Healthcare System. Venous samples were obtained at weekly visits to determine DHEA and DHEA-sulfate concentrations by radioimmunoassay.

RESULTS: Thirty-one subjects signed informed consent; 18 subjects quit smoking by self-report. Age-adjusted DHEA levels in smokers dropped an average of 0.6 ng/ml (CI = -1.3 ng/ml to 0.1 ng/ml; p=0.095) from baseline. Mean decreases from baseline in DHEA-S on weeks 1, 2, and 3 after quitting were 7%, 3%, and 16%, respectively.

CONCLUSIONS: These data from a small number of smokers are consistent with the hypothesis that smoking cessation is associated with a decrease in DHEA and DHEA-S shortly after smoking withdrawal. The decline in these
concentrations suggests that the management of the rate of decline in DHEA and DHEA-S concentrations may have a role in decreasing withdrawal symptoms and rates of relapses during smoking cessation. Larger investigational trials should be conducted to verify these hypotheses.

181. A pilot study on the impact of guideline implementation on the use of benzodiazepines in patients with a discharge diagnosis of alcohol withdrawal or delirium tremens. Barbara S. Chong, Pharm.D., Sarah K. Warren, M.D., Charles R. Bonapace, Pharm.D., Kit Simpson, Dr.P.H.; Medical University of South Carolina, Charleston, SC.

PURPOSE: To determine whether treating patients with benzodiazepines (BZDs) based on symptoms will optimize outcomes.

METHODS: A chart review was performed on all patients with a discharge diagnosis of alcohol withdrawal or delirium tremens prior to (July 1998 to February 1999, n=18) and following (March to June 1999, n=9) implementation of a treatment protocol based on Clinical Institute Withdrawal Assessment-Alcohol revised scores. The protocol was not applied during intensive care unit (ICU) stays. Data collected included demographics, daily lorazepam equivalents, days receiving benzodiazepines, length of stay (LOS), and outcome (e.g., seizure, hallucination). Data collection post-protocol is ongoing.

RESULTS: Pre-protocol versus post-protocol, patients were well matched by age and gender with LOS of 5 versus 8 days. The median lorazepam equivalents on days BZDs were administered were 4.2 and 9.9 mg/day pre-protocol and post-protocol, respectively. Although the median number of days receiving BZDs increased from 5 to 7 days post-protocol, the BZD days/LOS (%) decreased from 100% to 88%. Pre-protocol, 11% (2/18) of patients were admitted to the ICU versus 36% (3/9) post-protocol. For patients never treated in the ICU, the median lorazepam equivalents on days BZDs were given increased post-protocol from 4.2 to 5.3 mg/day (n=15 versus n=4), whereas the median BZD days/LOS (%) decreased from 100% to 50%. Seizure rates pre-protocol and post-protocol were 27% and 25%, respectively, while rates of delirium tremens declined post-protocol (40% versus 25%). Generally, restraint use, hallucinations and over-sedation increased post-protocol independent of whether patients were treated in the ICU.

CONCLUSIONS: Patients post-protocol had increased rates of admission to the ICU probably representing a sicker population. Trends were seen toward both improved and worsened outcomes post-protocol and additional post-protocol data is needed.

182E. Detection of the novel metabolite ethylphenidate after withdrawal or delirium tremens. E. Detection of the novel metabolite ethylphenidate after withdrawal or delirium tremens. John S. Markowitz, Pharm.D., Barry K. Logan, Ph.D., Fran Diamond, B.S., Kim Simpson, Dr.P.H.; Medical University of South Carolina, Charleston, SC.

PURPOSE: To determine whether the transsterification pathway known to convert cocaine (benzoylcgonine methyl ester) and ethanol to the toxic metabolite cocaethylene (benzoylcgonine ethyl ester) in humans will similarly convert structurally related methylphenidate (ritalinic acid methyl ester) to ethylphenidate (ritalinic acid ethyl ester) when dosed with ethanol.

METHOD: Postmortem blood samples from two methylphenidate/ethanol overdoses were analyzed by a method developed for this study. After solid phase extraction, samples were analyzed by liquid chromatography mass spectrometry using a deuterated internal standard and selected monitoring of analyte molecular ions.

RESULTS: This method provided a 0.5 ng/ml limit of quantitation for ethylphenidate and a calibration plot over the range of 0.005-5 ng/ml. Chromatograms were free of significant interferences. In case 1, ethylphenidate and methylphenidate blood concentrations were 8 and 310 ng/ml, respectively. In case 2, the corresponding values were 1 and 1600 ng/ml.

CONCLUSIONS: The new metabolite ethylphenidate was detected after fatal methylphenidate overdoses with ethanol coingestion. Ethylphenidate is an active catecholamine transporter inhibitory whose metabolic formation would be expected to contribute to central nervous stimulation, as well as to sympathomimetic side effects. The doses of methylphenidate and ethanol are unknown in the above two fatalities. The extent of ethylphenidate formation under controlled conditions is presently being investigated in human volunteers in order to establish whether this biotransformation pathway represents the basis of a potentially significant drug-drug interaction. Published in Clin Psychopharmacol 1999;19(4):362.

183. Effect of intensive pharmacist counseling in a university-based smoking cessation program. Sarah K. Chong, Pharm.D., Mary T. Roth, Pharm.D., Leslie J. Vollenweider, John M. Conry, Pharm.D., Tina J. Kanmaz, John S. Markowitz, Pharm.D., Kit Simpson, Dr.P.H.; Medical University of South Carolina, Charleston, SC.

PURPOSE: To determine whether counseling by a trained pharmacist or no counseling. Subjects were smokers smoking abstinence rates and depression in a university-based population.

METHODS: A chart review was performed on all patients with a discharge diagnosis of alcohol withdrawal or delirium tremens prior to (July 1998 to February 1999, n=18) and following (March to June 1999, n=9) implementation of a treatment protocol based on Clinical Institute Withdrawal Assessment-Alcohol revised scores. The protocol was not applied during intensive care unit (ICU) stays. Data collected included demographics, daily lorazepam equivalents, days receiving benzodiazepines, length of stay (LOS), and outcome (e.g., seizure, hallucination). Data collection post-protocol is ongoing.

RESULTS: Pre-protocol versus post-protocol, patients were well matched by age and gender with LOS of 5 versus 8 days. The median lorazepam equivalents on days BZDs were administered were 4.2 and 9.9 mg/day pre-protocol and post-protocol, respectively. Although the median number of days receiving BZDs increased from 5 to 7 days post-protocol, the BZD days/LOS (%) decreased from 100% to 88%. Pre-protocol, 11% (2/18) of patients were admitted to the ICU versus 36% (3/9) post-protocol. For patients never treated in the ICU, the median lorazepam equivalents on days BZDs were given increased post-protocol from 4.2 to 5.3 mg/day (n=15 versus n=4), whereas the median BZD days/LOS (%) decreased from 100% to 50%. Seizure rates pre-protocol and post-protocol were 27% and 25%, respectively, while rates of delirium tremens declined post-protocol (40% versus 25%). Generally, restraint use, hallucinations and over-sedation increased post-protocol independent of whether patients were treated in the ICU.

CONCLUSIONS: Patients post-protocol had increased rates of admission to the ICU probably representing a sicker population. Trends were seen toward both improved and worsened outcomes post-protocol and additional post-protocol data is needed.

184. Safety of bupropion in patients with co-existing medical and/or psychiatric conditions. Mary T. Roth, Pharm.D., Eric C. Westman, M.D., M.H.S.; University of North Carolina-Chapel Hill, Chapel Hill, NC; Durham VAMC; Duke University Medical Center, Durham, NC.

PURPOSE: Bupropion (Zyban®) has been shown to be an effective agent for smoking cessation. However, prior studies have primarily involved generally healthy smokers. The purpose of this study was to describe our experience with bupropion in smokers who have co-existing medical and psychiatric diseases.

METHODS: Subjects were referred by their physician for treatment with bupropion 150 mg twice daily for 8 weeks. Subjects had to be smoking at least 10 cigarettes/day and motivated to quit smoking. Exclusion criteria included a history or presence of seizures, anorexia, bulimia, and current use of a bupropion hydrochloride, a MAO inhibitor, or nicotine replacement therapy. Telephone follow up was performed by a pharmacist on or around the quit date and periodically thereafter for 8 weeks. Subjects returned to clinic for an 8-week and a 6-month follow up.

RESULTS: Seventy subjects met both inclusion and exclusion criteria and were treated with bupropion Ninety-six percent were men with a mean age of 54.0 years (SD = 10.1) who smoked a mean of 20.8 cigarettes per day (SD = 13.0). Sixty-four percent had a history of psychiatric disorders, including depression, post traumatic stress disorder, and bipolar disorder. Mild adverse effects (dry mouth, insomnia, bad taste) were noted in approximately 14% of subjects. One subject with bipolar disorder experienced precipitation of his mania on 150 mg twice daily of bupropion which resolved after reducing his dose to 100 mg daily.

CONCLUSIONS: Bupropion appears safe for smoking cessation in patients with co-existing medical and psychiatric conditions; however, careful monitoring may be prudent in those with underlying agitation, irritability, and mania.

Transplantation/Immunology


PURPOSE: To determine the influence of pharmaceutical care services on renal transplant patients’ systolic and diastolic blood pressures.

METHODS: Renal transplant patients at the Medical College of Georgia Renal Transplant Clinic were prospectively randomized into an intervention group or a control group. Patients in the intervention group received pharmaceutical care services which included ongoing medication reviews, with emphasis on preventing or resolving medication-related problems and providing pharmacotherapy recommendations. Patients in the intervention group interacted with the renal transplant clinical pharmacist at least monthly. Patients in the control group received routine clinic services but had no clinical pharmacist interaction. At each clinic visit, patients in both arms of the study underwent a physical exam which included blood pressure measurements. Analysis to detect differences in baseline and quarterly systolic and diastolic blood pressures between the intervention and control groups was performed for all patients who were enrolled in the trial for at least 15 months.

RESULTS: Thirty-three patients were included in the analysis, 18 in the intervention group and 15 in the control group. The groups were similar in sex and the number of hypertensive patients, and baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP). Patients in the intervention group had a mean SBP/DBP change of -8 mm Hg/-6 mm Hg compared to -2 mm Hg/-6 mm Hg in the control group. Analysis of variance showed a significant intervention group effect (p=0.017).

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2 mm Hg, -12 mm Hg/7 mm Hg, -11 mm Hg/9 mm Hg, and -7 mm Hg/4 mm Hg for the first, second, third and fourth quarters of the study, respectively. Subjects in the control group had a mean SBP/DBP change of -6 mm Hg/1 mm Hg, -48 mm Hg/33 mm Hg, -48 mm Hg/22 mm Hg, and -40 mm Hg/15 mm Hg for the first, second, third and fourth quarters of the study, respectively. No significant differences in change scores from baseline for SBP and DBP were observed at the final quarter. Significant differences in change scores from baseline for SBP and DBP between the intervention and control groups were observed at the second, third, and fourth quarters of the study (p<0.05).

CONCLUSION: Renal transplant clinic patients who received pharmaceutical care services in addition to routine clinic services had greater reductions in blood pressure than patients who did not receive pharmaceutical care services. Pharmaceutical care services in a renal transplant clinic have a positive impact on patients' blood pressure control.

186. Absence of nephrotoxicity with the concomitant use of amphotericin B lipid complex and cyclosporine. Steven P. Gelone, Pharm.D., the CLEAR™ database, Muralikrish S. Golconda, M.D., Stephen C. Rayhill, M.D., Reginald Frye, Pharm.D., Ph.D., Kimberly L. Napoli, Ph.D., Lisa Kalloch, B.S.N., Barry D. Klawans, Ph.D., M.D., University of Texas-Houston, Houston, TX; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Transplant patients who receive the immunosuppressive agent cyclosporine are at risk for fungal infections that may require treatment with amphotericin B. Although both drugs are nephrotoxic, the impact of the concurrent use of cyclosporine and amphotericin B lipid complex (ABLC) has not been assessed.

METHODS: The CLEAR™ database, representing data from patients treated with ABLC since commercial release, was queried to identify patients who concomitantly received cyclosporine. Creatinine values were assessed prior to and at the completion of therapy to assess the nephrotoxicity potential of combination therapy.

RESULTS: Data were available from 2285 patients treated with ABLC since January 1996. Of these, 427 (19%) also received concomitant cyclosporine. Of the 427 patients, 236 (56%) underwent recent allogeneic stem cell transplantation, while 116 (27%) had a solid transplant. ABLC was given empirically to 44% (189/427), while 66% received drug for a specific fungal diagnosis most often aspergillosis (103/427, 24%) or candidiasis (110/427, 26%). The median dose of ABLC was 4.8 mg/kg/day (range 0.7-11.2 mg/kg/day) for a median duration of 17 days (range 4-201 days). For all patients who received concomitant cyclosporine, the median baseline serum creatinine was 1.5 mg/dl (range 0.7-7.1 mg/dl) and the median end-of-treatment creatinine was 1.7 mg/dl (range 0.7-10.7 mg/dl). For allogeneic stem cell transplant recipients who received both drugs, despite receiving an average duration of ABLC treatment of 19 days, the median change in creatinine was only +0.3 mg/dl.

CONCLUSIONS: Concomitant ABLC and cyclosporine administration in the treatment of fungal infections is tolerated without significant increases in serum creatinine.

187. Comparison of the pharmacokinetics of rapamycin liquid and tablet formulations in renal transplant recipients. Patrick A. Kelly, Pharm.D., Regnald Frye, Pharm.D., Ph.D., Kimberly L. Napoli, Ph.D., Lisa Kalloch, B.S.N., Barry D. Klawans, Ph.D., M.D., University of Texas-Houston, Houston, TX; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Clinical trials investigating the new immunosuppressant rapamycin (Rapamune®) have thus far utilized an oil-base liquid formulation (L-RAPA). Recently, a new tablet formulation of rapamycin (T-RAPA) has begun clinical trials. In this study, we compared the steady-state pharmacokinetics of L-RAPA to that of T-RAPA administered de novo to renal transplant recipients.

METHODS: Subjects were randomized to receive either L-RAPA (n=33) or T-RAPA (n=31) as part of a multicenter clinical trial comparing the efficacy of the two formulations. At our center, 24-hour pharmacokinetic profiles were conducted after two weeks of de novo rapamycin dosing (2 mg q24h). Whole-blood samples were drawn immediately prior to and at 1, 2, 3, 5, 8, 12, and 24 hours post-dosing. Rapamycin concentrations were determined by HPLC. Comparisons between L-RAPA and T-RAPA were by Student's t-test.

RESULTS: The RAPA AUC0-24 of L-RAPA was similar to that of T-RAPA (145.5 ± 103.5 vs 152.1 ± 51.9 ng•hr/ml, respectively) suggesting similar relative bioavailability. Additionally, there were no differences between the two formulations in Cmax, Cmin, Cmax/Cmin, or Cmax/C0. There was, however, a significant difference in the percent fluctuation between the observed Cmax and C0 values for the two formulations. L-RAPA fluctuation was higher at 223 ± 127.2% compared to 221 ± 63.2% for T-RAPA (p<0.02).

CONCLUSIONS: Steady-state pharmacokinetic parameters for L-RAPA were not different when compared to those of T-RAPA. However, the lower percent fluctuation of T-RAPA may provide more consistent immunosuppressive exposure over the dosing interval and over the long-term.

188. Efficacy of daclizumab versus muromonab CD3 in preventing acute rejection in kidney and kidney/pancreas transplant recipients at high risk of allograft dysfunction. J. Michael Park, Pharm.D., M.S.; David I. Min, Pharm.D., M.S., Muralikrish S. Golconda, M.D., Stephen C. Rayhill, M.D., You-Min Wu, M.D.; University of Iowa, Iowa City, IA.

PURPOSE: To compare the efficacy of daclizumab (DCZ) and muromonab CD3 (OKT3) in preventing acute rejection (AR) when used as an induction agent in kidney and kidney/pancreas transplant recipients, thought to be at risk for delayed allograft function or AR.

METHODS: We retrospectively reviewed 199 cadaveric kidney and kidney/pancreas transplant cases (age 18 years) in University of Iowa Hospitals and Clinics from January 1996 to February 1999. Patients who received investigational immunosuppressants were excluded. By protocol for high-risk group, either OKT3 (5 mgqday for 7-10 days) or DCZ (2 mg/kg body weight immediately prior to transplant, followed by 1 mg/kg body weight on post-operative day 5) was initiated and cyclosporine or tacrolimus was deferred until allograft function was improved. Main outcomes measured were incidence of AR and infection during the first 3 months after transplantation.

RESULTS: A total of 64 patients (32 in DCZ, 32 in OKT3) met the selection criteria. The two groups were comparable with regard to gender, number of patients receiving multiple transplantation, and immunosuppressive regimen. Mean ages of patients in the two groups were different (45.9 ± 13.6 years [DCZ] vs 38.2 ± 8.0 years [OKT3], p<0.05).

Although there was a trend toward lower incidence of AR in DCZ, it did not reach statistical significance (p<0.05). One patient in DCZ lost a kidney due to ischemic damage from severe hypotension on post-operative day 16 compared to none in OKT3. There were no patient deaths in either group during the first 3 months.

CONCLUSIONS: In kidney or kidney/pancreas transplant recipients at high risk of allograft dysfunction, induction therapy with DCZ was as efficacious as that with OKT3 in prevention of AR without increasing incidence of infection during the first 3 months. A further study on cost effectiveness of DCZ versus OKT3 is ongoing.

189. The comparison of mycophenolate mofetil to azathioprine for the prevention of acute graft rejection in transplant patients. Jung M. Oh, Pharm.D., Paul J. Weidle, Pharm.D., Anne M. Wiland, Dave Klassen, M.D., University of Maryland Medical System.

PURPOSE: The study was performed to compare the efficacy of mycophenolate mofetil (MMF) and azathioprine (AZA) as a standard immunosuppressive regimen for the prevention of acute allograft rejection during the first 6 months after simultaneous pancreas kidney (SPK), pancreas after kidney (PAK) or pancreas transplant alone (PTA) pancreas transplantation.

METHODS: In this case-controlled study, MMF is compared to historical controls of AZA in the prevention of acute pancreas rejection in two different but comparable periods for patients receiving pancreas transplantation. The primary endpoint was treatment failure, defined as the occurrence of biopsy proven graft rejection, graft loss, patient death, or discontinuation of the study drug. Adverse drug events or infection during the first 6 months after transplant were also compared.

RESULTS: A total of 101 pancreas transplant patients were evaluated. In addition to AZA (n=57) or MMF (n=44), patients received calcineurin inhibitors (CsA or tacrolimus), corticosteroid, and antilymphocyte therapy (OKT3 or ATGAM) as part of triple immunosuppression. Comparison for the primary efficacy endpoint showed that significantly fewer (p<0.05) proportion of patients had biopsy proven rejection episodes during the first 6 months after transplantation with MMF (46%) than with AZA (69%). Time to biopsy proven rejection episode or treatment failure was longer for MMF versus AZA. Patients in the AZA group received a greater number of full courses of antirejection treatment as compared with the MMF. At 6 months after transplant, graft and patient survival were similar between the groups. Overall, the frequency of adverse events and discontinuation from the study drugs were similar between the groups, although MMF group experienced higher incidence of gastrointestinal adverse events and CMV disease.

CONCLUSION: MMF significantly reduced the rate of biopsy proven rejection episodes during the first 6 months after pancreas transplantation and was well tolerated.

190. Evaluation of the efficacy and cost of cytomegalovirus immune globulin after lung transplantation. Deb S. Sherman, Pharm.D., Douglas N. Fish, Pharm.D., Tony N. Hodges, M.D., Marty R. Zamora, M.D.; University of Colorado Health Sciences Center, University Hospital, Denver, CO.

PURPOSE: Cytomegalovirus (CMV) is a major cause of morbidity following lung transplantation (LTX) with an incidence of 60-85%. A pilot study was designed to determine the cost-effectiveness of CMVIG in preventing CMV infection after LTX.

METHODS: A retrospective case-controlled analysis of all LTX between 1992 and 1998 was performed. Patients expiring less than 30 days after or prior to discharge from the LTX admission, or at low risk for CMV infection (CMV-negative donor and recipient) were excluded. All patients received CMV
ACCP 1999 ANNUAL MEETING ABSTRACTS

190. Conversion from Sandimmune® to SangCyA® and Neoral® oral solution: results of a double-blind, randomized, crossover study of cyclosporine pharmacokinetics in stable cardiac allograft recipients. Jeffrey A. Haroldson, Pharm.D., Kathleen D. Lake, Pharm.D., Marc R. Pritzker, M.D., Robert W. Emery, M.D.; University of Michigan Medical Center, Ann Arbor, MI; Abbott Northwestern Hospital/Minneapolis Heart Institute, Minneapolis, MN.

PURPOSE: SangCyA® is an FDA-approved modified cyclosporine (CyA) formulation rated AB to Neoral® oral solution. SangCyA® and Neoral® have been shown to be bioequivalent in healthy volunteers and in renal and hepatic transplant patients but both have higher bioavailability than Sandimmune®. We assessed CyA pharmacokinetics (PK) in transplant patients when they were receiving Sandimmune® and after conversion to SangCyA™ and Neoral®.

METHODS: Stable cardiac transplant patients on Sandimmune® were assigned to receive SangCyA® and Neoral® in a double-blind, randomized, single-center, crossover study. Steady-state CyA PK were evaluated after administration of Sandimmune®, SangCyA® and Neoral®. PK parameters were derived from CyA levels (measured by TDX assay) collected over 12 hours. RESULTS: Seven (7) stable cardiac transplant recipients (4M/3F; mean ± SD age 60 ± 5 years) were studied. All patients were receiving stable CyA (Sandimmune®); dosages prior to enrollment. There were no significant differences in the first year post-transplant. Combination therapy of CyA with ganciclovir provides cost-effective prophylaxis for CMV following LTX.

CONCLUSIONS: SangCyA™ and Neoral® oral solutions demonstrate similar PK of CyA and its metabolites, as well as similar clinical tolerability in stable LT recipients. Bioequivalence has been demonstrated between SangCyA™ and Neoral® in this patient population.

METHODS: SangCyA™ and Neoral® were administered in a randomized, double-blind, 2-period crossover study. Each period consisted of 7 days of SangCyA™ or Neoral® at the same dosage. PK of CyA and its metabolites were measured using an HPLC assay. After day 15, the second assigned formulation was administered for 12 months in a blinded fashion for evaluation of long-term tolerability. RESULTS: Twenty-six patients were enrolled and 21 have completed 12-month follow up. At enrollment, age (mean ± SD) was 53 ± 10 years, and the mean time posttransplant was 5.5 years. Mean PK parameters of CyA, AM1, and AM9 are shown below. There were no significant differences (p>0.05). Anovol between SangCyA™ and Neoral®.

PK Parameters SangCyA® Neoral® p value

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CyA (n=22)</th>
<th>AM1 (n=22)</th>
<th>AM9 (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>460 ± 141</td>
<td>221 ± 123</td>
<td>460 ± 141</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>T90% (h)</td>
<td>4.1 ± 0.9</td>
<td>4.1 ± 0.9</td>
<td>4.1 ± 0.9</td>
</tr>
</tbody>
</table>

There have been no graft losses or allograft rejections during the 12-months following transplants. Mean ± SD CyA daily dose (mg/day), serum creatinine levels (mg/dl), ALT (u/L), and bilirubin (mg/dl) were similar between SangCyA™ and Neoral®.

CONCLUSIONS: SangCyA™ and Neoral® demonstrate comparable PK of CyA and its metabolites, as well as similar clinical tolerability in stable LT recipients. The results suggest that these two CyA formulations are interchangeable.

191E. Bioequivalence between two modified cyclosporine oral solutions (SangCyA™ and Neoral®) regardless of assay methodology or ingestion of a high fat meal. Gary L. Chan, Pharm.D., William Irish, Ph.D., Daniel M. Canafax, Pharm.D., SangStat Medical Corporation, Menlo Park, CA.

PURPOSE: We undertook this study to determine what, if any, effect assay methodology had on determination of bioequivalence between two modified cyclosporine (CyA) oral solutions (SangCyA™ and Neoral®). METHODS: A randomized, 3-period crossover study was conducted in 19 healthy volunteers. In each crossover period, each subject received a single 500 mg dose of CyA oral solution: SangCyA™ after a high-fat meal, Neoral® after a high-fat meal, or SangCyA™ under fasting conditions. Serial blood samples were collected, and whole blood CyA concentrations were determined using TDX, EMIT, and HPLC/MS/MS.

RESULTS: Mean ± SD CyA pharmacokinetic parameters, as measured by 3 different assays, for the 3 treatments were: SangCyA™ and Neoral® under fed conditions, and between SangCyA™ under fasted and fed conditions. TDX and EMIT yielded blood CyA concentrations that were 50% and 15%, respectively, higher than HPLC/MS/MS.

CONCLUSIONS: SangCyA™ and Neoral® oral solution were bioequivalent in healthy volunteers, regardless of the CyA assay method used. Moreover, high-fat meal ingestion does not significantly affect CyA absorption after oral administration of SangCyA™.

Presented at the Minneapolis Transplant Congress, Minneapolis, MN, October 20-23, 1999.


PURPOSE: We evaluated the pharmacokinetics (PK) of cyclosporine (CyA) and its metabolites and assessed the clinical tolerability after long-term administration of SangCyA™ and Neoral® in stable liver transplant (LT) recipients. Bioequivalence has been demonstrated between SangCyA™ and Neoral® in this patient population.

METHODS: SangCyA™ and Neoral® were administered in a randomized, double-blind, 2-period crossover study. Each period consisted of 7 days of SangCyA™ or Neoral® at the same dosage. PK of CyA and its metabolites were measured using an HPLC assay. After day 15, the second assigned formulation was administered for 12 months in a blinded fashion for evaluation of long-term tolerability.

RESULTS: Twenty-six patients were enrolled and 21 have completed 12-month follow up. At enrollment, age (mean ± SD) was 53 ± 10 years, and the mean time posttransplant was 5.5 years. Mean PK parameters of CyA, AM1, and AM9 are shown below. There were no significant differences (p>0.05). Anovol between SangCyA™ and Neoral®.

PK Parameters SangCyA® Neoral® p value

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CyA (n=22)</th>
<th>AM1 (n=22)</th>
<th>AM9 (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>211 ± 177</td>
<td>15 ± 0.7</td>
<td>75 ± 35</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>4.1 ± 0.9</td>
<td>4.1 ± 0.9</td>
<td>4.1 ± 0.9</td>
</tr>
<tr>
<td>T90% (h)</td>
<td>4.1 ± 0.9</td>
<td>4.1 ± 0.9</td>
<td>4.1 ± 0.9</td>
</tr>
</tbody>
</table>

CONCLUSIONS: SangCyA™ and Neoral® demonstrate comparable PK of CyA and its metabolites, as well as similar clinical tolerability in stable LT recipients. The results suggest that these two CyA formulations are interchangeable.

Presented at the 19th Annual Meeting the American Society of Transplantation, Chicago, IL, May 15-19, 1999.

Women's Health


PURPOSE: To characterize intra- and inter-subject and diurnal variability in peak expiratory flow rates (PEFR) of healthy non-asthmatic females over at least one complete uninterrupted menstrual cycle; to determine whether a relationship exists between PEFR and premenstrual symptoms in healthy non-asthmatic females; to provide a unique opportunity to educate female pharmacy students via interactive study participation.

METHODS: Forty healthy non-asthmatic female pharmacy students were enrolled and 31 (age 22.1 ± 1.5 years, mean length of menstrual cycle 29.0 ± 2.3 days) completed the study. During the longitudinal, investigator-blinded, 9-week study, the subjects were followed for two menstrual cycles with at least one uninterrupted cycle. Throughout the study period, each woman recorded premenstrual symptom questionnaire scores (15 mood and physical symptoms, graded 0-3 severity) daily. The subjects also measured and recorded PEFR (three consecutive attempts) every morning and every evening.

RESULTS: Over half of the subjects (58.1%) showed classic patterns of premenstrual symptoms, whereas PEFR fluctuated randomly over the course of the cycle. The average coefficients of variation (CV) for intra-subject variability were 4.17 ± 2.09% for morning PEFR, 3.97 ± 2.25% for evening PEFR, and 3.72 ± 2.55% for mean daily PEFR. The CV for inter-subject variability were 4.17 ± 2.09% for morning PEFR, 3.97 ± 2.25% for evening PEFR, and 3.72 ± 2.55% for mean daily PEFR. The average absolute diurnal variation was 17.13 ± 12.46 L/min and the relative diurnal variation was 3.98 ± 2.52%. Only 14 of 24 (11.3%) correlations between

Irrespective of the assay used, bioequivalence was demonstrated between SangCyA™ and Neoral® under fed conditions, and between SangCyA™ under fasted and fed conditions. TDX and EMIT yielded blood CyA concentrations that were 50% and 15%, respectively, higher than HPLC/MS/MS.

CONCLUSIONS: SangCyA™ and Neoral® oral solution were bioequivalent in healthy volunteers, regardless of the CyA assay method used. Moreover, high-fat meal ingestion does not significantly affect CyA absorption after oral administration of SangCyA™.
PEFR and premenstrual symptoms were significant (p<0.05). CONCLUSIONS: Intra- and inter-subject variability in PEFR is minimal in non-asthmatic females, similarly, diurnal variation in PEFR also is low. The menstrual cycle appears to have little effect on pulmonary function in healthy non-asthmatic females. Pharmacy students who take part in serial PEFR monitoring gain a new appreciation for asthma and asthmatic patients.

Clinical Pharmacy Forum

These abstracts describe the delivery, development, justification, or documentation of innovative clinical pharmacy services; they may be descriptive only and need not contain an evaluative component.

194. A retrospective analysis of cisapride use in an adult ambulatory population: implications for formulary removal. Martin R. Giannamore, Pharm.D., Bella Mehta, Pharm.D., Ruth E. Emptage, Pharm.D.; The Ohio State University, Columbus, OH.

PURPOSE: This drug use evaluation (DUE) was conducted to monitor physicians’ adherence to the manufacturer’s warnings, precautions, and contraindications regarding cisapride use in our health care network.

METHODS: Medical records of 23 patients receiving cisapride were retrospectively evaluated for the following parameters: presence of interacting drugs (as listed in the prescribing information); presence of disease states or conditions for which cisapride is contraindicated or likely to increase the risk of cardiac dysrhythmias; and, documented trial of alternative GI medications (e.g., metoclopramide, H2-antagonists, proton pump inhibitors).

RESULTS: Drug interaction data was classified as follows: two patients (9%) were receiving concomitant agents which could have produced major (life-threatening) interactions; three patients (13%) were receiving agents which could have produced moderate (increasing morbidity) interactions; and, thirteen patients (57%) were receiving agents which could have produced minor interactions. Four patients (17%) had drug-disease interactions which increase the risk of cardiac dysrhythmias. Cisapride was utilized as a first-line inhibitor. Four patients (17%) had drug-disease interactions which increase the risk of cardiac dysrhythmias. Cisapride was utilized as a first-line agent for the treatment of gastroesophageal reflux disease (GERD) in 13 (57%) of patients evaluated.

CONCLUSION: The use of cisapride in our population placed a substantial number of patients at risk for drug-drug and drug-disease interactions. This data was presented to the Pharmacy and Therapeutics Committee and resulted in removal of cisapride from the formulary. In addition, this DUE provides opportunities for medical staff education regarding drug interactions and the pharmacotherapy of GERD.

195. Utilization of glycoprotein IIb/IIIa receptor antagonists, its relationship to patient characteristics and outcomes. Judy W. M. Cheng, Pharm.D., BCPP, Karin A. Greenberg, Pharm.D., Bernard Mehl, DPS, Mount Sinai Medical Center, New York, NY; Long Island University, Brooklyn, NY.

PURPOSE: To describe the utilization of glycoprotein IIb/IIIa inhibitors (GP2b3a) in a tertiary care center; to evaluate whether patient characteristics, cardiovascular risk factors, and coronary interventions affect physicians’ selection of GP2b3a. To justify the necessity for maintaining three GP2b3a on formulary.

METHODS: Medical records of 100 patients admitted with acute ischemic coronary syndrome (AICS) were reviewed. Patient demographics, past medical history, coronary intervention and outcomes were recorded. These parameters were compared among groups using chi squared or ANOVA.

RESULTS: Important demographics, coronary intervention and outcomes are summarized below. Patients who received 2 GP2b3a were in a research study. Data reviewed that our institution is a high volume intervention center. Most GP2b3a were used for procedures. If abciximab and either eptifibatide or tirofiban were kept on formulary, a cost of $1500 per 100 patients will be saved with abciximab and eptifibatide based on our population.

<table>
<thead>
<tr>
<th>Abciximab (n=29)</th>
<th>Eptifibatide (n=29)</th>
<th>Tirofiban (n=29)</th>
<th>Abciximab + Tirofiban (n=48)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 13</td>
<td>66 ± 13</td>
<td>69 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Framingham risk</td>
<td>12 ± 3</td>
<td>11 ± 5</td>
<td>10 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>score for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>developing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ischemic heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>29 ± 7</td>
<td>42 ± 7</td>
<td>46 (abciximab)</td>
<td>NS</td>
</tr>
<tr>
<td>AICS</td>
<td>0 ± 0</td>
<td>6 (tirofiban)</td>
<td>16 (tirofiban)</td>
<td>NS</td>
</tr>
<tr>
<td>Angioplasty, stent,</td>
<td>26 ± 6, 40</td>
<td>6 ± 7, 10</td>
<td>35, 36, 8, 6</td>
<td>13, 11, 2, 2</td>
</tr>
<tr>
<td>atelectores,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dyspnea</td>
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<td>1, 0, 0</td>
<td>2, 2, 1, 4</td>
<td>0, 1, 1, 2</td>
</tr>
<tr>
<td>Arrhythmia, major</td>
<td>33%</td>
<td>33%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>bleeding, death,</td>
<td>33%</td>
<td>33%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Patient characteristics, risk factors and interventions did not determine selection of GP2b3a. Since we are a primary intervention institution, maintaining all three agents on formulary may not be justified.

196. An innovative pharmacy program improves management of cholesterol in patients with coronary artery disease. Lisanne DiTusa, Pharm.D., Aileen Berezowsky, Pharm.D., Marc Rehant, G. Parsley, B.S., Brian D. Snyder, M.D.; State University of New York at Buffalo; Health Care Plan, Buffalo, NY.

METHODS: To assess the impact of a pharmacy-based cholesterol management program in a health maintenance organization.

RESULTS: A retrospective analysis of cisapride use in an adult ambulatory population showed only 50% of patients had appropriate FLP monitoring by their physician. 60% of patients were receiving cholesterol medication and 33% of patients had achieved target cholesterol. Four months after program implementation, FLPs were available for >96% of patients, 72% of patients were on medication and 71% were at target cholesterol, with mean (SD) LDL of 90 (18). This was associated with a mean increase in drug costs of $3 per patient per month.

CONCLUSION: Capitalizing on the pharmacist-patient interaction in this setting provides improved cholesterol management in a large number of CAD patients with a minimal increase in drug cost.

197. Impact of pharmacist home visits on medication appropriateness in geriatrics. Michele A. Scriccengost-Kibbee, B.S., Richard J. Pachci, Pharm.D., FCCP, Amy L. Tuttie MBA; University of Pittsburgh Medical Center, Pittsburgh, PA.

High medication use in the elderly increases their risk of receiving inappropriate drugs or experiencing drug-related problems (DRPs). The Living-at-Home Program (LAHP) is a case management program for individuals >70 years old living in the Pittsburgh area that has existed for eleven years and has recently added a pharmacist to the staff.

PURPOSE: Evaluate the impact of a pharmacist making home visits on medication appropriateness.

RESULTS: In the first five months of the program, 116 visits have been made to patients. The mean MAI score at baseline was 13.0 ± 3.1, which improved to 10.5 ± 2.8, representing a 19.2% change. The most common DRPs were untreated problems (1.7%), improper drug selection (1.7%), failure to receive drug (2.2%), overdose (0.86%), adverse drug reactions (1.7%) and drug use with poor indication (0.86%). Barriers to compliance included lack of education about medications (36%), disorganization of medications (33%), physical/mental problems (33%), fear of adverse reaction to medication (13%) and pharmacy inconvenience (27%).

CONCLUSION: In home visits by a pharmacist help to improve medication appropriateness, and identify DRPs barriers to compliance for geriatrics in the home setting.

198. Evaluation of pharmaceutical care on hypertension and diabetes control in an urban outpatient medicine clinic. Sara L. Schroeder, Pharm.D., Kai Jan Cheang, Pharm.D., Thomas P. Lonergan, Pharm.D., BCPP, Yoon Kang, M.D.; Barnes-Jewish Hospital, St. Louis, MO; Washington University, St. Louis, MO.

PURPOSE: To determine the potential impact of pharmaceutical care on hypertension and diabetes control in an urban medicine clinic.

METHODS: The inclusion criteria of this pilot study were blood pressure ≥ 140/90 mm Hg (≥ 140/90 mm Hg in diabetic patients) and/or HgA1c > 8% or a blood glucose ≥ 140 mg/dl measured in the clinic. Patients were randomized to intervention or control. Pharmacists made pharmacotherapy recommendations to physicians and educated intervention patients on their disease and drug therapy. The control group received usual care provided by physicians. The primary outcome was percentage of patients meeting blood pressure (≤ 140/90 mm Hg or ≤ 120/85 mm Hg if diabetic) and HgA1c (< 8%); secondary outcomes were mean changes in above values.

RESULTS: Baseline characteristics were similar between groups with 49 and 40 patients in the intervention and control arms respectively. Patients were predominantly African-American with a mean age of 60 years. Intervention patients were seen an average of 2.5 times by a pharmacist, with an average follow-up of 126 days. At the end of the study, the percentage of hypertensive patients with blood pressure goal in the intervention arm was 21% in the control arm. The mean blood pressure reduction was 17/3 mm Hg vs 9/8 mm Hg in the intervention and control arms respectively. A minimal decrease...
CONCLUSION: ACEI therapy is well-utilized in the treatment of systolic failure by internal medicine physicians.

METHODS: Patients assigned an ICD-9 code for CHF from May 1998 to May 1999 were assessed for frequency of use and dose prescribed of angiotensin-converting enzyme inhibitors (ACEI). Patients had to be on ACEI for at least one year and already undergone dose titration. In addition, use of aspirin, lipid-lowering therapies, and other cardiovascular medications were evaluated. Ventricular ejection fractions (EF) were obtained via echocardiogram, MUGA or angiogram.

RESULTS: One hundred male patients (69.7 ± 9.8 years) were identified: 77% with ischemic cardiomyopathy, 23% with idiopathic cardiomyopathy, and 72% with systolic dysfunction. Of patients with ischemic disease, 66% were on aspirin, and 60% met an LDL goal of <100. The median daily doses of ACEI in systolic dysfunction were: captopril 150 mg, fosinopril 40 mg, lisinopril 40 mg. Of patients with systolic dysfunction not on warfarin, 40% had severe dysfunction (EF <25). The percent of patients, stratified by type of ventricular dysfunction, treated with each agent were: Type (EF) 80% (EF >35) 80% (EF >25) 72% (EF <25) 72% (EF <20). Diabetic (9) 55% 100% 11% 67% 33% 11% 44% Normal (19) 68% 100% 26% 37% 42% 21% 37%

CONCLUSION: ACEI therapy is well-utilized in the treatment of systolic dysfunction at our institution. However, concerns regarding appropriateness of digoxin and ACEI prescribing indicate the need for educational efforts to ensure optimal management of patients with CHF. Educational initiatives will be presented.

203. The development and implementation of an antibiotic surveillance program. Chelsea O. Church, Pharm.D., David W. Hawkins, Pharm.D., Holly E. Rogers, Pharm.D., candidate, A. Thomas Taylor, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This study evaluated utilization of perioperative beta-blockade in patients undergoing elective non-cardiac surgery. The purpose of the study was to evaluate the impact of selected antibiotics, evaluate students' antimicrobial therapy knowledge, and evaluate potential cost avoidance of interventions.

RESULTS: Of the 608 recommendations that were made, approximately 88.5% (n=537) were accepted by the medical teams. Improper medication selection (24%), untreated infection (23%), and increased cost (21%) were avoided, for a total of $5204, which accounted for approximately 66% of the medication-related problems. The most commonly accepted recommendations involved anti-infective (36%) and cardiovascular (17%) medications. Two pharmacists evaluated each accepted recommendation by using Hatoum's criteria for assessing potential impact on patient care. This evaluation indicated that 77% of the accepted recommendations would have a significant (56%), very significant (20%) or extremely significant (1%) potential impact on patient care outcomes.

CONCLUSION: During the 5-year study period, pharmacy students performed pharmaceutical care activities that had a positive impact on patient care.


PURPOSE: This study evaluated 5 years of pharmaceutical care provided by Doctor of Pharmacy (Pharm.D.) students on acute care clerkships at the Medical College of Georgia. Objectives of the study included: 1) teaching pharmacy students how to identify, document, solve, and prevent medication-related problems; 2) documenting the number and types of recommendations made by Pharm.D. students to medical teams; 3) determining the acceptance rate of these recommendations; and 4) determining the potential impact of students' recommendations on patient care.

METHODS: Seventy-seven Pharm.D. students enrolled at the University of Georgia College of Pharmacy were assigned to a general medicine or family medicine service at Medical College of Georgia Hospital during September 1994 through March 1999 were included in the study. Under the supervision of a faculty preceptor, the students were responsible for preventing and resolving patient medication-related problems and providing appropriate pharmacotherapy recommendations.

RESULTS: Of the 608 recommendations that were made, approximately 88.5% (n=537) were accepted by the medical teams. Improper medication selection (24%), untreated infection (23%), and increased cost (21%) were avoided, for a total of $5204, which accounted for approximately 66% of the medication-related problems. The most commonly accepted recommendations involved anti-infective (36%) and cardiovascular (17%) medications. Two pharmacists evaluated each accepted recommendation by using Hatoum's criteria for assessing potential impact on patient care. This evaluation indicated that 77% of the accepted recommendations would have a significant (56%), very significant (20%) or extremely significant (1%) potential impact on patient care outcomes.

CONCLUSION: During the 5-year study period, pharmacy students performed pharmaceutical care activities that had a positive impact on patient care.

201. Utilization of perioperative beta-blockade in elective non-cardiac surgery patients in a community hospital. Mary A. Miller, Pharm.D.; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; Talbert, Pharm.D., BCPS; South Texas Veterans Health Care System; Washington, DC, May 15-20, 1999.

PURPOSE: This prospective, naturalistic study, initiated November 1, 1996, was conducted to determine the utilization of beta-blocker therapy in patients undergoing elective non-cardiac surgery. The study was designed to contrast costs and efficacy associated with the initiation of the atypical antipsychotics risperidone and olanzapine.

METHODS: Two 6-month periods, prior and post antipsychotic initiation, were analyzed regarding costs and services utilized. The main questions posed were: 1) did these new agents 1) improve symptoms, 2) reduce utilization of high cost services, and 3) reduce overall expenditures, although the agents cost more than older, cheaper medications? To assess the impact on client symptoms, each psychiatrist quarterly scored the PANSS and AIMS.

RESULTS: Although the average olanzapine dose (n=127) 9%, tobramycin (n=14) 7%, trovafloxacin (n=3) 4% and vancomycin (n=26) 8%. Overall, inappropriate regimens (n=38) included 58% not switched to PO, 13% inappropriate dosages, 24% inappropriate schedules, 2.5% inappropriate indications, and 2.5% lacked serum levels. An estimated total cost avoidance of $5204 was documented. CONCLUSIONS: ASP was successful in improving students’ antimicrobial knowledge scores, potentially improved appropriateness of antibiotic therapy, and made a positive financial impact on the medical center.

200. Utilization of perioperative beta-blockade in elective non-cardiac surgery patients in a community hospital. Mary A. Miller, Pharm.D.; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; Talbert, Pharm.D., BCPS; South Texas Veterans Health Care System; Washington, DC, May 15-20, 1999.

PURPOSE: This study evaluated utilization of perioperative beta-blockade in patients undergoing elective non-cardiac surgery.

METHODS: A chart review of patients admitted to a community hospital for elective non-cardiac surgical procedures was undertaken. Patient charts were reviewed to identify those meeting criteria for perioperative beta-blockade. Criteria included known coronary artery disease or the presence of two or more coronary disease risk factors. Coronary disease included a history of myoccardial infarction or angiography and risk factors included age (>65 years), hypertension, hypercholesterolemia (>240 mg/dl), diabetes, or current smoking. Pre-hospital and in-hospital beta-blocker use was recorded as well as beta-blocker contraindications. Patient charts were also reviewed for documentation of post-operative myoccardial ischemia.

RESULTS: Of 116 consecutive patients admitted to a community hospital for elective non-cardiac surgery were reviewed. Thirty-one patients met the criteria for use of perioperative beta-blocker therapy. Seven patients had documented coronary artery disease and 24 had two or more risk factors for coronary disease. No patients received beta-blocker therapy postoperatively. Four patients received pre-operative labetolol for blood pressure control. Two of those patients met the criteria for perioperative beta-blockade and two did not. Beta-blocker therapy was contraindicated in one patient with coronary disease risk factors.

CONCLUSIONS: Beta-blocker therapy to prevent perioperative myocardial ischemia in patients with coronary disease or risk factors is underutilized. Efforts to improve beta-blocker utilization in this setting are warranted.
204. An innovative method for educating pharmacy students about alcohol pharmacokinetics and substance-related disorders. Bethany A. DiPaula, Pharm.D., University of Maryland, Baltimore, MD.

PURPOSE: Approximately 90% of adults have had some experience with alcohol, and a substantial number (60% of males, 30% of females) have had one or more alcohol-related adverse events. The lifetime prevalence of substance-related disorders varies by age and may range between 11.36% (males) and 35.54% (males). Pharmacists are exposed to substance-related disorders in patients, peers, family members, and potentially self. However, many pharmacists are poorly informed and therefore may feel uneasy. This laboratory provides a comfortable forum for discussion to educate pharmacy students about the absorption and elimination pharmacokinetics of alcohol. Information on diagnosis and management of substance-related disorders is conveyed through case presentations.

METHODS: Two students consent to drink 1-2 beers. Classmates obtain breath alcohol levels via a portable breathalyzer. The students complete anonymous pre and post-tests to assess educational value and attitudes. RESULTS: Thirty-three of 34 (97%) students surveyed had never used a breath analyzer to monitor BAL. Sixteen of 34 (47%) students reported that this laboratory would affect their personal drinking behaviors. Twenty-nine of 34 (85%) students commented that this exercise would affect their interaction with patients. The average didactic test scores increased from 52% to 75%.

CONCLUSIONS: Providing an interactive forum for discussion of substance-related disorders can teach new skills, change student attitudes towards alcohol consumption, and increase the comfort and educational level of future pharmacists.


PURPOSE: University of California San Francisco (UCSF) has utilized an antimicrobial order sheet (AOS) review system since 1990. Pharmacists screen all antimicrobial orders using P&T approved guidelines. We developed a case-based, interactive antimicrobial computer program to educate physicians in proper and efficient antimicrobial review. The program: (1) encompasses the necessary information for credentialling and provided a comfortable forum for discussion to educate pharmacy educators, and a physician designed and implemented this process. The committee conducted two grand rounds seminars. These seminars encompassed the necessary information for credentialling and provided category 1 continuing medical education credit. During the seminars, the audience received a pretest utilizing an audience response system, a review of thalidomide's history, an explanation of the S.T.O.P. system, and a question and answer session. The audience was given the opportunity to complete the test at a later date via the Internet. To provide credentialling to new prescribers and to update others, the pharmacy department developed an Intranet website dedicated to thalidomide.

207E. An online Doctor of Pharmacy program for pharmacy practitioners: development and evaluation of six courses. Christine K. O'Neil, Pharm.D., Therese I. Poller, Pharm.D.; Duquesne University, Pittsburgh, PA.

PURPOSE: The goals of this project were to: 1) develop an online Pharm.D. program that prepares practitioners with background and skills to provide pharmaceutical care; and 2) evaluate the impact of the program on the knowledge of participants, their preparedness to provide pharmaceutical care, and frequency of pharmaceutical care activities.

METHODS: Curriculum for six credits in a 38-credit program was developed. Content areas focused on clinical skills and pharmacotherapy of cardiovascular, endocrine, gastrointestinal, rheumatoid and respiratory patients. Instructional strategies consisted of self-study with PowerPoint presentations and readings, synchronous chat sessions with FDACS Intranet Client™, and case-based assignments. The impact of the project was evaluated in two ways. Upon entry into the program, participants completed a 70-item pretest of knowledge that reflected the content areas covered in the first six courses. Participants also completed a survey of their current pharmaceutical care activities, attitudes, and preparedness to provide specialty pharmaceutical care activities. Program effectiveness was evaluated comparing baseline scores of knowledge and survey results to scores upon completion of developed curricular content.

RESULTS: By the end of Spring 1999, 28 students completed courses in the program. There was significant improvement in test scores (p=0.0001) and participants' preparedness to provide specialty pharmaceutical care services (p=0.01).

CONCLUSIONS: The first six courses in the online program were successful in increasing the knowledge and preparedness to provide pharmaceutical care. The success of this project provided the stimulus for development of the entire Pharm.D. program. Presented at the 100th Annual Meeting of the American Association of Colleges of Pharmacy, Boston, MA, July 3-7, 1999.


Because transplantation is a highly specialized field that deals with a unique population of patients with remarkably individualized needs, it is most effectively managed by clinicians with specialty training in transplant. However, pharmacists in the community setting may be the primary health care contact with these patients as they dispense refills for medications. Providing quality pharmaceutical care to transplant patients may be a challenge to community pharmacists with regard to the complexity both of the literature and concepts of immunology, as well as the availability of specialty information in the core medical journals (i.e., N Engl J Med, JAMA). To ensure the delivery of specialty pharmaceutical care to transplant patients, a university-based transplant pharmacist certificate program was developed to strengthen expertise and competency in transplantation. Instructors for the program were selected based on their expertise in transplant and included distinguished physicians, university faculty and clinical specialists. Seven hours of didactic and experiential education were delivered to participants in the program, centering on the basics of immunology, drug interactions with immunosuppressants, complications of transplantation, and frequency of pharmaceutical care activities.

122 pharmacists nationwide (85% practiced in specialty pharmacies) completed the educational components of the program for continuing education credits. Of these, 86 pharmacists completed the examination process to be certificated, 88% of which passed the examination overall.


The incidence of Crohn's disease is estimated at 5/100,000 or 380,000 to 480,000 people. The cost of illness was over $1.7 billion or $9197 per patient annually. New medication, infliximab, was approved by the FDA for the
treatment of moderate to severely active Crohn's disease in patients with or without fistulas. However, the cost of infliximab therapy is very expensive, $2340 per treatment vs $941 for the standard therapy. Since the case mix in our institution is about 70% Medicare, the projected reduction in DRG reimbursement ranged from 25.5% to 47.3%.

PURPOSE: In order to provide the latest therapy and prevent hospitalization, we sorted inputs from GI clinic, patient billing service, quality assurance and the manufacturer (Centocor). Our decision is to implement an outpatient infliximab infusion program since there was minimal overheads incurred in the GI clinic and the manufacturer would provide support in billing reimbursement for patient assistant program.

METHODS: Pharmacy and GI service established the appropriate use criteria, standing orders, monitoring form for infliximab infusion. A process chart was mapped out to ensure prior authorization, facilitating ordering and applying for patient assistant program. From November 1998 to May 1999, 11 infusions were administered to 6 eligible patients.

RESULTS: No adverse drug reactions were observed in all the patients. One patient has complete closure of fistulas, diarrhea was halted in 2 patients. No need to follow up within 6 month. Since the program is ongoing, we will follow up the rest of the patients for their progress. In term of reimbursement, 10 treatments were approved and reimbursed; over 70% of the charge were covered. One claim was rejected due to inadequate documentation. (We have re-submitted the claim and await reimbursement). The outreach program was 1.5 month and collected $31,420.78. The return on investment was 71%.

CONCLUSION: In order to demonstrate the value of clinical pharmacy services, we need to participate in the business process to optimize cares and to ensure reimbursement for the institution. Overall, we think the infusion program is successful. And we will learn from this experience to foster other outpatient programs and grow the business.

210. The application of a pharmacoeconomic model to determine cost-effectiveness of academic detailing clinical pharmacy services in improving angiotensin converting enzyme inhibitor utilization in type-2 diabetes with albuminuria. Joseph J. Medics, Pharm.D., BCP, Elizabeth Jones, Pharm.D., BCNSP; Cathy Sinnott, B.S.N., Ruth Weinstock, M.D., Ph.D., Roy Guhary, Pharm.D., Dave Lehmann, M.D., Pharm.D.; University Hospital; State University of New York; Health Science Center at Syracuse, Syracuse, NY.

PURPOSE: Angiotensin converting enzyme inhibitors (ACEI) remain underutilized despite their well-documented efficacy in slowing the progression to endstage renal disease in diabetes with albuminuria. We developed a pharmacoeconomic Markov model which evaluated the impact of enhancing the utilization of ACEI in this population through clinical pharmacy services.

METHODS: In our clinic 232 patients had type-2 diabetes of which 47 had clinically significant levels of urinary albumin with a 48.9% utilization rate of ACEIs. ACEI utilization was assumed to improve to 80% with clinical pharmacy services. Transition probabilities between the Markov health states and utilities were derived from literature values. Sensitivity analysis varied ACEI utilization rates and success rates. Academic detailing clinical pharmacy services were considered cost-effective at a level of $50,000/QALY (quality adjusted life year).

RESULTS: Cost of care per year was $23,688 without clinical pharmacy services and $21,930 with such services. An addition of 0.2 quality adjusted life years was gained by the addition of ACEI. Our analysis revealed a potential savings of $7,972 per QALY ranging from $3,295 to $12,171.

CONCLUSIONS: Academic detailing clinical pharmacy services could be cost-saving in the ambulatory care type-2 diabetics in a primary care setting even with modest improvements in the utilization of ACEI. Validation of pharmacist success rates of ensuring ACEI therapy constitutes our next phase of study.

211. Improving the utilization and effectiveness of HMG-CoA reductase inhibitors in patients with coronary artery disease. Kathleen Wooley, Catharine Acosta, Pharm.D., Michelle Faulkner, Pharm.D., Daniel E. Hillman, Pharm.D.; Creighton University, Omaha, NE.

PURPOSE: Despite overwhelming evidence that the HMG-CoA reductase inhibitors (statins) reduce the risk of cardiovascular morbidity and mortality, utilization of this class of drugs in high-risk coronary artery disease (CAD) patients is erratic. We evaluate the ability of a post-hospital discharge intervention aimed at prompting physicians to improve the utilization and effectiveness of statins in CAD patients.

METHODS: The baseline (control) population included 303 consecutive CAD patients admitted to the coronary care unit (CCU) of our teaching hospital from 10/01/98 through 12/31/98. The intervention group included 309 consecutive CAD patients admitted to the CCU from 01/04/99 through 03/31/99. Intervention patients had follow-up letters sent to their physicians with patient-specific recommendations concerning lipid therapy at 2, 8 and 12 weeks after hospital discharge.

RESULTS: Utilization and outcome of lipid-lowering therapy in the two groups is summarized below.

| Number of | Lipid Status | LDL-C Titrated | Patients | Achieved Initial Dose | Treated | 212E. Training future faculty members: the addition of a teaching/learning component to a residency program. Nancy W. Wang, Pharm.D., Eric H. Hobson, Ph.D.; Albany College of Pharmacy, Albany, NY.

PURPOSE: Although residency/fellowship programs provide practice and research training, practitioners and pharmacy practice faculty start their teaching careers with little-to-no teaching/learning training. Yet they are expected to teach in classrooms and practice settings, often without additional teaching support. To remedy this situation an existing ambulatory care residency program was modified to include pedagogical training in adult learning and application of these principles in both the didactic and clinical teaching settings.

METHODS: The addition of a teaching/learning specialist to the ACP faculty provided an opportunity to incorporate training in adult teaching/learning into a rural ambulatory care residency program. The teaching/learning components include: information processing and acquisition; child-adult learning differences; teaching/learning adaptation to the teaching/learning contexts; and formative and summative assessment techniques. Application opportunities include developing patient education materials and programs, implementing case-based, small group pharmaco-therapeutics classes, participating in ongoing teaching research, and teaching/assessing learning in other courses.

RESULTS: Recruitment for the 1999 residency cycle yielded qualified and motivated candidates. Deans and division directors from other colleges of pharmacy who have followed this program's development wish to recruit the program's graduates. External requests for financial support have met with interest.

CONCLUSIONS: As demands on practitioners and faculty increase and recruitment becomes more difficult, advanced training in teaching/learning via a combined residency program is ideal for the graduate, health-care institutions and colleges of pharmacy. Presented at the 100th Annual Meeting of the American Association of Colleges of Pharmacy, Boston, MA, July 3-7, 1999.

212. Use of weight-based heparin dosing nomograms in a community teaching hospital. Anne M. Stoyich, Pharm.D., Fred Massoomi, Pharm.D., Paul A. Danelas, Pharm.D.; Nebraska Methodist Hospital, Omaha, NE.

PURPOSE: To minimize the risk of thromboembolism and bleeding by promptly achieving and maintaining the targeted therapeutic APTT range using weight and diagnosis based heparin dosing nomograms.

METHODS: A medication utilization evaluation (MUE) was conducted in a community hospital prior to and following initiation of weight based heparin nomograms. A low dose nomogram for treatment of AF, CP, CVA, and AMI...
215. Pharmaceutical care for HIV-infected patients in transition between health care delivery settings. Kimberly K. Summers, Pharm.D., Thomas C. Hardin, Pharm.D.; South Texas Veterans Health Care System; University of Texas Health Science Center at San Antonio, San Antonio, TX; University of Texas at Austin, TX.

PURPOSE: To describe a pharmaceutical care program for providing continuity of care for HIV-infected patients with critical drug therapy transitions, including dispensing, counseling, and coordination with the outpatient pharmacy for commercially unavailable medications prior to final FDA approval. The pharmacist works directly with the primary care physician to provide case management and medication reconciliation. Approximately 30-40% of the patients scheduled for the clinic are seen every day. A multidisciplinary team, consisting of physicians, nurses, and nutritionists, works together to assess patients for the need of nutritional support, develop a nutritional plan, monitor nutrition intake, and follow-up with patients. The intranet site was developed to standardize the care of patients with critical drug therapy transitions and nutritional needs. A comprehensive intranet site was developed to standardize the care of patients with critical drug therapy transitions and nutritional needs. The development of an intranet site to standardize the care of patients receiving nutritional support was identified as a quality improvement initiative within the institution. A comprehensive intranet site was developed by a multidisciplinary group consisting of pharmacists, gastroenterologists, dietitians, nephrologists, and nutritional support nurses. The intranet site consists of the following components: nutritional assessment, nutritional plan development, nutrition monitoring, and specific disease states. An in-depth review and recommendations of nutritional support in patients with pulmonary disease, liver disease, pancreatic disease, malabsorptive disease, renal disease, and refeeding syndrome is described. Surgical and medical attending staff and residents will be educated on the use of the intranet site. Following implementation, a retrospective review of 200 patients, 100 patients before and after the implementation of the intranet site, will be evaluated. Patients will be reviewed for satisfaction and appropriateness of enteral and parenteral nutrition. Efficacy, length of stay, length of nutritional therapy, complications, and total hospital and nutrition costs will be collected. It is hypothesized that education through the use of an available intranet site located on each unit will improve the selection and appropriateness of nutritional support with decreased costs.

218. Implementation of a multidisciplinary-developed intranet site for the management of nutritional support at Scott & White Memorial Hospital. Annie Herrington, Pharm.D., BCPS, Kim Culp, M.D., Donald Rawls, M.D., Tim Pflanzer, M.D., Glen Willis, M.D., Eileen Dietzker, M.S., R.D., C.N.S., Jim Mendenhall, B.S.N., C.N.S.N., Catherine Arnold, M.S., R.D.; Scott & White Memorial Hospital, Temple, TX.

The development of an intranet site to standardize the care of patients receiving nutritional support was identified as a quality improvement initiative within the institution. A comprehensive intranet site was developed by a multidisciplinary group consisting of pharmacists, gastroenterologists, dietitians, nephrologists, and nutritional support nurses. The intranet site consists of the following components: nutritional assessment, nutritional plan development, nutrition monitoring, and specific disease states. An in-depth review and recommendations of nutritional support in patients with pulmonary disease, liver disease, pancreatic disease, malabsorptive disease, renal disease, and refeeding syndrome is described. Surgical and medical attending staff and residents will be educated on the use of the intranet site. Following implementation, a retrospective review of 200 patients, 100 patients before and after the implementation of the intranet site, will be evaluated. Patients will be reviewed for satisfaction and appropriateness of enteral and parenteral nutrition. Efficacy, length of stay, length of nutritional therapy, complications, and total hospital and nutrition costs will be collected. It is hypothesized that education through the use of an available intranet site located on each unit will improve the selection and appropriateness of nutritional support with decreased costs.

219. Development and implementation of a medication management program in a pediatric attention deficit hyperactivity disorder clinic. Tracy M. Hagemann, Pharm.D., Stacy Schrader, Pharm.D., Mary Beth Logue, Ph.D.; University of Oklahoma, Oklahoma City, OK.

PURPOSE: To describe the development and implementation of a medication management program in a pediatric attention deficit hyperactivity disorder (ADHD) clinic and the outcomes.

METHODS: A psychologist and pediatric medical resident-run ADHD clinic was begun at a university teaching hospital in July 1997. The clinic meets twice a week in this being developed in two phases. Phase I included initial set-up and education of providers in diagnostic skills. Phase II is the development of treatment and monitoring guidelines. Clinical pharmacy services was contacted to help draft medication documentation and practice guidelines to educate providers on medications used to decrease polypharmacy and diminish medication adverse effects in this population. Treatment algorithms were developed to include initial choice of
medication, dose and regimen adjustments. Wall charts were created for identifying and minimizing medication adverse effects. A patient medication profile was included in the patient's clinic chart. A clinical pharmacist attended the clinic weekly. Patient charts were reviewed for medication use. The survey will be re-administered to assess the acquisition of information essential for appropriate management of ADHD in pediatric primary care settings.

CONCLUSION: This pediatric ADHD medication program promotes medication management and is a method of educating health care providers on appropriate evaluation, dosage adjustment, follow up and provision of medication education to their patients.


PURPOSE: This is a prospective trial to determine the influence of clinical pharmacist involvement on health care outcomes in renal transplant patients. Pharmaceutical care objectives included: (1) identifying, documenting, solving, and preventing medication-related problems; (2) documenting the number and types of recommendations made by the clinical pharmacist to the clinician's physicians; (3) determining the physician acceptance rate of these suggestions; and (4) determining the potential impact of the clinical pharmacist's recommendations on patient health care outcomes.

METHODS: The renal transplant pharmacist performed medication reviews and was responsible for preventing or resolving patients' medication-related problems and providing appropriate pharmaceutical recommendations for renal transplant patients seen in the Medical College of Georgia Renal Transplant Clinic. All recommendations and interventions that were made by the renal transplant clinical pharmacist from October 1997 to May 1999 were classified according to medication-related problem and class of medication. Two pharmacists (other than the renal transplant pharmacist) independently evaluated each accepted recommendation by using Hatoum's criteria for assessing potential impact on patient care.

RESULTS: Eight-hundred and forty-four recommendations were made during the 18-month study period, and approximately 96% (n=811) of the recommendations were accepted by the clinician's physicians. Untreated indication (28%), overdose (27%), and subtherapeutic dosage (18%) accounted for greater than 70% of the medication-related problems. The most commonly accepted recommendations involved immunosuppressant (33%) and cardiovascular (28%) medications. Over 95% percent of the recommendations were judged to have a significant (76%) or a very significant (22%) potential impact on patient health care outcomes.

CONCLUSION: During the first 18 months of renal transplant clinical pharmacy services, the pharmacist performed pharmaceutical care activities that were well received by the clinic's physicians and had a positive impact on patient health care outcomes.

223. Development, implementation, and evaluation of a compliance management service. Lorinda Rasor Babb, Pharm.D., Ruth E. Empgate, Pharm.D.; The Ohio State University, Columbus, OH.

PURPOSE: The purpose of this study is to develop and implement a pharmacist-based compliance management service and evaluate its effectiveness through documented changes in refill histories, measurable treatment outcomes, and frequency of health care utilization.

METHODS: Physicians, nurses, and pharmacists at two outpatient clinic systems refer patients for potential enrollment. The pharmacist administers a detailed questionnaire that assesses barriers to compliance. For each compliance issue identified, the pharmacist makes patient-specific interventions. The patient returns at least monthly until compliance goals are achieved. At each visit, compliance is evaluated through refill histories and measurable treatment outcomes. The pharmacist's satisfaction on the timely patient visits, emergency room visits, and hospitalizations is also collected.

RESULTS: To date, ten patients are enrolled in the service. Data for six patients after at least 3 months of compliance counseling demonstrate a change in the prescription refill rate from 67.5% to 69.3%. The following average changes in treatment outcomes were observed: systolic blood pressure +1 mm Hg (6 patients); diastolic blood pressure + 6 mm Hg (6 patients); pulse -5.8 beats per minute (four patients); fasting blood glucose -103 mg/dl (two patients). From 3 months prior to 3 months after counseling, physician visits per patient decreased from 1.8 to 1.7.

CONCLUSIONS: Preliminary results suggest that individualized medication compliance counseling improves compliance, improves treatment outcomes, and decreases physician visits. Collection of outcome data will continue as more patients are enrolled in the service. Future applications include utilizing the data to establish justification for reimbursement.

224. Cost justification of a scheduled refill service for patients in a university-based pharmaceutical care center. Nancy L. Shapiro, Pharm.D., BCPS, Sara Samuel, Pharm.D. candidate, Mark Kliethermes, MBA; University of Illinois at Chicago, Chicago, IL.

PURPOSE: The purpose of this study is to measure the financial performance of a scheduled refill service (Refill-10) for patients that receive ten or more chronic prescriptions per month from the Pharmaceutical Care Center. Patients are seen monthly by an assigned pharmacotherapist by appointment to help coordinate care, organize prescription refills, encourage compliance, provide patient education, minimize pharmacy visits, and to maximize patient outcomes.
METHODS: Currently, five half-days of a pharmacists’ time are devoted to providing care to Refill-10 patients. All prescriptions are processed on the evening shift 1-2 days before the scheduled appointment. One-month prescription data for 105 patients from September 1998 was analyzed to retrieve actual reimbursements, acquisition cost of drugs, and net profit. Annual projections were made using the September data. Actual one-year reimbursements, and profits will be presented. Continued enrollment has been occurring, with 130 current patients.

RESULTS: Preliminary results indicate the 105 enrolled patients in September filled 1314 prescriptions, with an average of 12.5 prescriptions per patient. Total reimbursements were $64,796, with total monthly profits of $11,896, averaging $617 revenue/patient, and $113 profit/patient. Annual projections using the 105 patients indicated total revenues of $777,575, and profits of $145,254, averaging $1,383/patient. These profits more than offset their costs to provide the service.

CONCLUSIONS: The Refill-10 Service is a profit-generating program. Annual projected profits are sufficient to justify the pharmacist’s time. Increasing the number of patients in the program will likely increase profits to the pharmacy.


PURPOSE: The central focus in treating psychiatric patients is on the management of psychiatric symptoms, often with less attention given to physical disease. Many psychotropic drugs contribute to sedation, serum lipid changes, and weight gain. These factors present barriers to adopting a healthy lifestyle. This drug use evaluation prompted the development of a dyslipidemia clinic and evaluated current dyslipidemia management at Northwest Missouri Psychiatric Rehabilitation Center. Findings were compared to Adult Treatment Panel III (ATP-III) guidelines to assess level of care and quality of dyslipidemia care.

METHODS: Thirty-one patients were identified from February 1, 1998 to February 1, 1999 who had lipid levels above the goal levels described in ATP-III guidelines. Data was collected by retrospective chart review and included demographics, concurrent medications, labs, and dietary status.

RESULTS: Seven patients (22.6%) were identified as having no coronary heart disease (CHD) and < 2 risk factors. Six of those (85.7%) had appropriate treatment with four (60%) reaching desired lipid goals. Twenty-one patients (67.9%) had no CHD and > 2 risk factors. Seventeen of those (81.8%) received appropriate treatment. Of nineteen patients treated a minimum of 6 months with medications, diet, or a combination of both, seven (36.8%) reached their desired lipid levels. Three patients (9.7%) had CHD and all received appropriate therapy, with only one reaching goal.

CONCLUSION: The average percentage of patients reaching their desired lipid goals was higher (44.4%) as compared to the general population (25%). Given these findings, this psychiatric population showed a more favorable response to dyslipidemia management and monitoring than the general population.

226. A survey of atypical antipsychotic prescribing trends. Jackie Y. Raskind, Pharm.D., Sheila R Botts, Pharm.D., BCPP, Hillside Hospital, Glen Oaks, NY; St. John’s University, Jamaica, NY.

PURPOSE: This survey assessed atypical antipsychotic prescribing trends in order to 1) document extent of atypical utilization and agent selection in specific patient populations; 2) evaluate factors influencing antipsychotic selection; 3) describe utilized sources drug information; 4) evaluate knowledge base of cost and side effect profile; 5) describe dosing strategies, adequate medication response time, off-labeled use and polypharmacy regimens.

METHODS: A 34 item anonymous questionnaire was distributed to all psychiatrists (n=253) employed at a private, university-affiliated, non-profit psychiatric institution. Surveys were distributed at an administrative meeting and via inter-office mail.

RESULTS: Approximately 50% (126/253) of psychiatrists responded. Risperidone and olanzapine were the most common antipsychotic agents selected in first episode, chronic schizophrenia with positive or negative symptomatology, geriatric and pediatric populations. History of treatment response (85%), side effect profile (79%), personal experience with the agent (75%) were considered very important factors in antipsychotic selection. The majority of respondents (77%) indicated that their journal articles were their most utilized and influential sources of new drug information followed by hospital sponsored continuing education (38%), and peer discussion (25%). Only 22-36% of psychiatrists correctly identified the atypical antipsychotic cost, most often underestimating. Thirty-five percent of psychiatrists prescribed titrated olanzapine every three days. Sixty-four percent of respondents combine typical and atypical antipsychotics.

CONCLUSIONS: Atypical antipsychotics are used first line in all schizophrenia populations. Physician education is needed in the area of anti-psychotic selection.


PURPOSE: We wish to determine antidote preparedness of Illinois hospitals for nine crucial antidotes. METHODS: In July 1998, the Illinois Poison Center (IPC) surveyed 201 Illinois hospitals with emergency departments. Quantities of the following antidotes were requested: crotalidae antivenin, cyanide kit, deferoxamine, digoxin immune-Fab, ethanol 10%, fomepizole, glucagon, pralidoxime, and IV pyridoxine. Amounts were compared to suggested minimum stock quantities as published in the 1997 IPC Antidote Chart. We tabulated the range, median, number of hospitals with no stock, and number meeting minimum suggestions.

RESULTS: Data were obtained from the 147 responding hospitals.

<table>
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<tr>
<th>Antidote</th>
<th>Median</th>
<th>Range</th>
<th>Minimum</th>
<th>Maximum</th>
<th>0 to 20 vials</th>
<th>0 to 4 kits</th>
<th>0 to 168 vials</th>
<th>0 to 35 vials</th>
<th>0 to 30 liters</th>
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<tr>
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CONCLUSION: Our data demonstrate inadequate antidote stocking in many Illinois hospitals. Treatment with these nine antidotes can be life-saving, and time does not permit transferring patients or borrowing drugs from alternate sources when critically poisoned patients need treatment. We urge hospital pharmacy managers nationwide to evaluate current inventories of these crucial antidotes.


PURPOSE: To describe the types of clinical and economic interventions performed by transplant pharmacists in solid organ transplant recipients.

METHODS: An interim analysis of a multicenter, prospective study of transplant pharmacists interventions was conducted to describe the types of interventions led by the pharmacists. The study population consisted of solid organ transplant recipients enrolled in a pharmacy service specific to transplant disease management. A pre-tested pharmacist intervention documentation (PID) form was used to record the types of interventions encountered in organ transplant recipients. The transplant pharmacists documented the type of intervention, recommendations, actions taken, and anticipated outcomes. More than one type of intervention may have been discovered at a particular consultation. All PID forms completed between October 1996 and May 1999 were considered for this analysis. Descriptive statistics were used to summarize the results.

RESULTS: PID forms were completed by transplant pharmacists among four geographically dispersed transplant centers. A total of 513 (26%) of the pharmacy consultations were for interventions that were related to medication regimens (21.1%), appropriate therapeutic selection (33.7%), compliance (11.3%), cost (20.1%), and adverse effect (10.3%). Of the interventions were in transplant recipients who had been transplanted for kidney (81.5%), kidney/pancreas (9.5%), liver (7.3%), or heart (1.8%) organs. Sixty-five percent of the interventions were conducted within one year and 43% within six months post-transplantation.

CONCLUSIONS: Pharmaceutical care in organ transplant recipients resulted in interventions that had both clinical and economic implications. This study emphasizes the importance of transplant disease management post solid organ transplantation.

Research Institute

The following papers, based on Fellowships and Research Awards provided by the ACCP Research Institute, will be presented. Full titles and authors are listed, although a complete abstract may not be available for all papers at the time of this printing.

228. Bayer Critical Care Fellowship: Oxandrolone use in trauma patients. Jane M. Gervasio, Pharm.D., Roland N. Dickerson, Pharm.D., Jessica Swearing (17%), Mark E. Yates, Pharm.D., Timothy C. Fabian, M.D., Martin A. Croce, M.D., Rex O. Brown, Pharm.D.; University of Tennessee, Memphis and Regional Medical Center at Memphis, Memphis, TN.
POURPOSE: The erosion of body cell mass in patients following multiple trauma has been reported. The effect of oxandrolone (Ox) on nutritional and wound outcome following multiple trauma was studied.

METHODS: Patients who were injured and required enteral nutrition (EN) were randomized to receive either Ox 10 mg BID or placebo (P) for a maximum of 28 days. Total urinary nitrogen (TUN), nitrogen balance, and body cell mass were measured on day 1 of EN, and then at days 7, 10, and 10 study exit. Patients were assessed daily for infectious complications. Body cell mass was measured by BIA and TUN was measured by chromoluminiscence.

RESULTS: Sixty multiple trauma patients were entered into the study; 30 in each group. Baseline groups were similar for patient demographics and each group was not significantly different between groups. Nitrogen balance was not positive at study days 7, 10, and 10 in each group. The body cell mass decreased slightly in both groups over the first 10 days. Prealbumin serum concentrations increased significantly in both groups at days 10 and study exit when compared to study entry. There was no significant difference between groups for length of hospital stay, length of ICU stay, and incidence of pneumonia or sepsis.

CONCLUSION: Oxandrolone does not demonstrate obvious benefit in nutritional and clinical outcome during the first month following multiple trauma.
PURPOSE: NQO1 (NAD(P)H:quinone oxidoreductase) is a flavoprotein that catalyzes the two-electron reduction of quinones and their derivatives. Since quinones are known constituents of cigarette smoke and implicated in the pathogenesis of lung cancer, our hypothesis is that NQO1 activity is increased in NSCLC. The purpose of this study is to evaluate NQO1 activity by gene expression and mutation status in NSCLC and matched normal tissue.

METHODS: Matched biopsy samples (tumor and normal margins) were obtained from 50 patients undergoing resection of their primary tumor. RNA was isolated by standard techniques and quantitated spectrophotometrically. Gene expression is quantitated by RT-PCR (reverse transcription-polymerase chain reaction) with a competitive, reaction specific internal standard and analysis by capillary electrophoresis with laser induced fluorescence (CE-LIF). Mutation at bp609 is evaluated by restriction fragment polymorphism (RFLP) with analysis by CE-LIF.

RESULTS: All 50 subjects have been recruited to the protocol. Gene quantitation is currently available for 18 subjects. The mean gene expression in the normal lung tissue is 7.4 x 10^{-15} ng/ml ± 0.7 and the mean gene expression in the NSCLC 8.2 x 10^{-13} ± 163 ng/ml (p=0.08). NQO1 gene expression in normal lung tissue ranged from 0-1.88 x 10^{-14} ng/ml and from 0-5.13 x 10^{-12} ng/ml in the tumor tissue. One subject did not express NQO1 in either the tumor or the normal tissue.

CONCLUSION: NQO1 gene expression is similar in normal lung tissue. NQO1 was overexpressed and highly variable in tumor samples. Results are trending towards a significant difference between NQO1 gene expression in normal tissue and matched lung samples. This may represent an important avenue for exploration in the pathogenesis of lung cancer and drug selectivity as quinones such as MMC are activated by NQO1 and may be preferentially activated where NQO1 is overexpressed.
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