Late Breakers, I  
Activity No. 0217-0000-10-098-L01-P

Monday, October 18  
9:15 a.m.–10:45 a.m.  
Convention Center: Room 16

Moderator: LeAnn B. Norris, Pharm.D., BCPS, BCOP  
Clinical Assistant Professor, Department of Clinical Pharmacy and Outcomes Sciences, South Carolina College of Pharmacy, Columbia, South Carolina

9:15 a.m.  
Cardiovascular Therapeutics  
*Larisa H. Cavallari, Pharm.D., FCCP, BCPS*  
Associate Professor, Department of Pharmacy Practice, University of Illinois at Chicago, College of Pharmacy, Chicago, Illinois

9:30 a.m.  
HIV  
*Frank Romanelli, Pharm.D., MPH, BCPS*  
Associate Dean and Associate Professor of Pharmacy, Health Sciences, and Medicine, University of Kentucky, Lexington, Kentucky

9:45 a.m.  
Ambulatory Care  
*Jill S. Burkiewicz, Pharm.D., BCPS*  
Professor of Pharmacy Practice, Midwestern University–Chicago, College of Pharmacy, Downers Grove, Illinois

10:00 a.m.  
Critical Care  
*Sara D. Brouse, Pharm.D., BCPS*  
Associate Professor, Texas Tech University of Health Sciences Center, School of Pharmacy, Dallas, Texas; Advanced Practice Pharmacist, Critical Care/Cardiology, VA North Texas Healthcare System, Dallas, Texas

10:15 a.m.  
Medication Safety  
*Francesca E. Cunningham, Pharm.D.*  
Residency Program Director, Veterans Health Administration and PBM, Center for Medication Safety, Hines, Illinois

10:30 a.m.  
Psychiatry  
*Tawny B. Smith, Pharm.D.*  
Director, Psychiatric Pharmacy Program, University of Texas, College of Pharmacy, Austin, Texas

Faculty Conflict of Interest Disclosures

Sara D. Brouse: no conflicts to disclose  
Jill S. Burkiewicz: no conflicts to disclose  
Larisa H. Cavallari: no conflicts to disclose  
Francesca E. Cunningham: no conflicts to disclose
Learning Objectives

1. Describe a ‘late breaking’ HIV related therapeutic report.
2. Describe limitations in the HIV-Ab response.
3. Define ‘broadly neutralizing Abs (BN Abs).’
4. Discuss implications of newly discovered BN Abs.
5. Evaluate the clinical literature comparing dopamine versus norepinephrine for shock reversal and apply the evidence to clinical practice in the ICU.
6. Compare/contrast the adverse effects of dopamine and norepinephrine described in the SOAP-II trial.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Objectives

- Describe a 'late breaking' HIV related therapeutic report.
- Describe limitations in the HIV-Ab response.
- Define ‘broadly neutralizing Abs (BN Abs).’
- Discuss implications of newly discovered BN Abs.

Neutralizing Antibodies A Step Forward?

- Recognition that ‘early’ Abs are particularly ineffective
- Major impediment in vaccine development
- Thailand vaccine trial: 30% reduction in infection rates (p>0.05)/vaccine abandoned
- Previously 'broadly neutralizing Abs' (BN Abs) defined by ability to negate ~ 40% of HIV strains

Disclosures

The presenter has no disclosures to report regarding this presentation.


Neutralizing Antibodies

- Long recognized that most HIV targeted Abs do not sufficiently neutralize HIV
- Focus on critical Ab sites associated with minimal mutations
- Donor 45 (AA male with long-standing HIV): probed for BN Abs
- Three unique BN Abs identified (VRC01, VRC02, VRC03)
Neutralizing Antibodies

Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01.

- BN Abs active against an unprecedented 90% of HIV strains (notably inclusive of almost all sexually transmitted strains)
- VRC01: gp120 specific, avoids confirmationally fluid areas of binding site, not affected by glycan shielding, lacks any auto-reactivity
- Source of 'elite control'?

Viral Spiking

Credit: NIAID VRC

Challenges

- Illicit Ab production in sufficient quantity
- Illicit Ab response in a timely fashion (within the window of opportunity)

Clinical Implications

- Exogenous administration of Abs (passive immunization) – perinatal transmission?
- Ab infused microbicides
- Vaccine development (active immunization)
- Gene therapy

HIV Vaccine Research ‘Renaissance’

Closing in on HIVs Achilles Heal?

“We are going to be at this a whole before any clinical benefits are realized.”

- Gary Nabel, MD, PhD
Background

- National Osteoporosis Foundation:1
  - Recommends adequate calcium intake of at least 1,200 mg daily, including supplements if necessary, for those age 50 and older
  - Vitamin D intake of 800-1000 international units
- Consider not only impact on bone health, but overall patient health

Calcium & Vascular Disease:

Pros

- Cardiovascular (CV) risk factors
  - Calcium supplementation ↑ HDL levels1
  - Small, transient decreases in blood pressure2
- Observational studies
  - Inverse relationship between calcium intake and:
    - Ischemic stroke3
    - Ischemic heart disease mortality4

Cons

- Randomized, controlled trial with CV events pre-specified as secondary endpoints1
  - Postmenopausal women randomized to calcium supplementation (citrate 1g) or placebo for 5 years
    - Increased risk of MI (RR 2.12, 95% CI 1.01-4.47)
- Supplementation acutely ↑ serum calcium2
  - ↑ serum calcium levels are a CV risk factor3
  - Evidence of vascular calcification in patients with renal disease on calcium supplementation4

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis


Study Objective & Design

- Objective:
  - To investigate whether calcium supplements increase the risk of cardiovascular disease.
- Design:
  - Meta-analysis
  - Patient-level and trial-level data
Methods:
Inclusion/Exclusion Criteria

- **Inclusion Criteria:**
  - Randomized, double-blind, placebo-controlled
  - 100 or more participants
  - Duration ≥ 1 year
  - Elemental calcium ≥ 500 mg/day
  - Baseline mean age > 40 years
  - Female or male participants
- **Exclusion Criteria:**
  - Calcium + Vitamin D v. placebo
  - Included if vitamin D given to comparator group
  - Dietary calcium or nutritional supplements only
  - Systemic disease other than osteoporosis

Outcomes:
Cardiovascular Events

- **Primary endpoints:**
  - Time to 1st myocardial infarction
  - Time to 1st stroke
  - Time to 1st cardiovascular event
  - Composite endpoint: myocardial infarction, stroke, sudden death
- **Secondary endpoint:**
  - All-cause mortality

Search Results

- Over 11,000 articles identified
- 190 articles screened
- 15 studies eligible for inclusion

Analysis

- Reported patient-level and trial-level data separately
- Tests for heterogeneity
- Cox proportional hazards model
  - Adjusted for possible covariates associated with CV outcomes:
    - Age, sex, smoking status, history of DM, DL, HTN or CHD at baseline
  - Pre-specified subgroup analyses:
    - Dietary calcium, age, sex, Vitamin D status (≥~20 ng/mL or <~20 ng/mL), supplement type
- Publication bias assessed

Trial Characteristics

- 15 studies eligible for inclusion
  - 5 studies with patient-level data (n>8,000)
  - 6 studies with only trial-level data (n~3800)
  - 4 studies with trial-level data had no data on CV outcomes
  - Calcium supplementation ranged from 500 mg to 2 g daily
  - 9/11 studies used doses of 1 g or more
  - Mean trial duration ~ 4 years
  - Endpoints typically BMD or fracture

Baseline characteristics: Patient-level analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Calcium Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>74.5 years (70-79)</td>
<td>74.6 years (71-79)</td>
</tr>
<tr>
<td>Women</td>
<td>76.5%</td>
<td>76.2%</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>97.2%</td>
<td>97.2%</td>
</tr>
<tr>
<td>Weight, mean (SD)</td>
<td>68.4 kg (14.1)</td>
<td>67.9 kg (13.7)</td>
</tr>
<tr>
<td>Dietary calcium, mean (SD)</td>
<td>837 mg/day (377)</td>
<td>831 mg/day (370)</td>
</tr>
<tr>
<td>25-OH Vitamin D, mean (SD)</td>
<td>26.4 ng/mL (11.6)</td>
<td>25.7 ng/mL (11.5)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11.0%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28.0%</td>
<td>28.4%</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>8.1%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Hypolipidemia</td>
<td>14.8%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.0%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>
Results

<table>
<thead>
<tr>
<th></th>
<th>Patient-level data</th>
<th>Trial-level data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 studies, n=8151</td>
<td>8 studies, n=6116</td>
</tr>
<tr>
<td>MI</td>
<td>1.31 (1.02-1.67)*</td>
<td>1.27 (1.01-1.59)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.20 (0.96-1.50)</td>
<td>1.12 (0.92-1.36)</td>
</tr>
<tr>
<td>Composite MI, stroke, sudden death</td>
<td>1.18 (1.00-1.39)</td>
<td>1.12 (0.97-1.30)</td>
</tr>
<tr>
<td>Death</td>
<td>1.09 (0.96-1.23)</td>
<td>1.07 (0.96-1.19)</td>
</tr>
</tbody>
</table>

*NNH=69

Subgroup Analysis:
Dietary Calcium Intake
Pre-specified subgroup analysis

<table>
<thead>
<tr>
<th>Dietary calcium intake</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Above median (&gt;805 mg/day)</td>
<td>1.85 (1.28-2.67)</td>
</tr>
<tr>
<td>Below median (&lt;805 mg/day)</td>
<td>0.98 (0.69-1.38)</td>
</tr>
</tbody>
</table>

Author’s conclusions

- Treatment of 1000 people with calcium for 5 years:
  - Causes 14 additional myocardial infarctions
  - Prevents 26 fractures
- Supplementation of calcium without coadministered vitamin D is associated with an increased risk of MI
- Reconsideration of the role of calcium supplementation in prevention and treatment of osteoporosis is needed

Discussion: Limitations

- NOF recommends adequate calcium AND vitamin D
- Meta-analysis excluded studies that included vitamin D
- High dietary calcium intake
- Trials did not have CV events specified as the primary endpoint
- Incomplete data in 15% of participants

Vitamin D & CV Health

- In observational studies, Vitamin D deficiency is associated with CV disease and multiple CV risk factors
- Women’s Health Initiative
  - Coadministration of calcium 500 mg + vitamin D 200 IU BID had no effect on CHD or stroke risk
  - Patient population differed from current meta-analysis

Clinical Applicability

- Assess dietary intake of calcium and vitamin D prior to recommending supplementation
- Take an active role in reducing CV risk factors for all patients

References:

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Sara Brouse, Pharm.D., FCCP, BCPS, AG Cardiology
Associate Professor of Pharmacy Practice
Advanced Practice Pharmacist in Critical Care/Cardiology
TTUHSC School of Pharmacy/VA North Texas Medical Center

Catecholamine Receptor Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>α₁</th>
<th>β₁</th>
<th>β₂</th>
<th>DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine (DA)</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine (NE)</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
</tbody>
</table>

Surviving Sepsis Campaign 2008

- Maintain MAP ≥ 65mmHg. (1C)
- Norepinephrine or Dopamine centrally administered are the initial vasopressors of choice. (1C)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock. (2C)
- Vasopressin 0.03 units/min may be subsequently added to norepinephrine


Dopamine Metabolism

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Study Objective

- To evaluate whether norepinephrine could reduce death rates in patients with shock more than dopamine

Methods: Study Design

- Prospective, Double-blind, Randomized, Multicenter trial
- Study period 28 days
- December 2003 to October 2007 in Belgium, Austria, & Spain
- 1679 Medical/Surgical ICU patients in whom a vasopressor was required for shock syndrome

Inclusion Criteria

- > 18 years old
- Vasopressor agent needed for treatment of shock
  - “Shock” defined as mean arterial pressure (MAP) less than 70mmHg or systolic blood pressure (SBP) < 100mmHg despite “adequate” fluid resuscitation and signs of tissue hypoperfusion
  - “Adequate” fluids defined as > 1000mL of crystalloids or 500mL of colloids

Exclusion Criteria

- Less than 18 yrs old
- Already received a vasopressor agent for > 4 hours during current shock episode
- Serious arrhythmia
  - Atrial fibrillation with heart rate > 160 bpm
  - Ventricular tachycardia
- Declared braindead

Methods

- Dopamine dosed at 2mcg/kg/min & titrated by increments of 2 until max 20mcg/kg/min
- Norepinephrine dosed at 0.02mcg/kg/min & titrated to max 0.19mcg/kg/min
- Prior vaspressors were discontinued (if received) and transitioned to study drug
- Lack of efficacy: open label norepinephrine added
- Weaning: open-label weaned 1st, then study drug
- 28-day study period

Endpoints

- Primary endpoint
  - Mortality at 28 days
- Secondary endpoints
  - ICU mortality / Hospital mortality
  - ICU length of stay
  - Number of days without need for organ support
  - Time to hemodynamic stability
  - Use of dobutamine or other inotropics
  - Adverse effects
Statistics

- Estimated 765 patients/group for 80% power to show 15% mortality difference
- Predefined boundaries for early discontinuation
  - Superiority of norepinephrine over dopamine
  - Superiority of dopamine over norepinephrine
  - No difference between dopamine or norepinephrine
- 1st endpoint: unadjusted chi square
- 2nd endpoints: unpaired student’s t-test or wilcoxon rank-sum test
- Cox proportional-hazards regression model

Methods: Study Design

Results: Primary Endpoint

<table>
<thead>
<tr>
<th>Time period</th>
<th>DA</th>
<th>NE</th>
<th>Odds Ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Mortality</td>
<td>50.2%</td>
<td>45.9%</td>
<td>1.19 (0.98-1.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>59.4%</td>
<td>56.6%</td>
<td>1.12 (0.92-1.37)</td>
<td>0.24</td>
</tr>
<tr>
<td>28-Day Mortality</td>
<td>52.5%</td>
<td>48.5%</td>
<td>1.17 (0.97-1.42)</td>
<td>0.10</td>
</tr>
<tr>
<td>6-Month Mortality</td>
<td>63.8%</td>
<td>62.9%</td>
<td>1.06 (0.86-1.31)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Results: Secondary Endpoints

- Achievement of MAP goal of 65 (mean +/- SD)
- DA 6.3 ± 5.6 hrs vs NE 6 +/- 4.9 hrs
- Support-free days through day 28
  - Vasopressors: DA 11 days vs NE 12.5 days
  - Mech vent: DA 8.5 days vs NE 9.5 days
  - ICU not needed: DA 8.1 days vs NE 8.5 days

Results: Standard of Care

- Fluids
  - Day 1 DA received more than NE
- Hydrocortisone use:
  - DA 344 (40.1%) vs NE 326 (39.7%)
- Drotrecogin alfa use (septic shock):
  - DA 102 pts (18.8%) vs NE 96 pts (19.1%)
- *Open-label NE: DA 26% vs NE 20%
Results: Safety

<table>
<thead>
<tr>
<th>ADRs</th>
<th>DA, no. (%)</th>
<th>NE, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>207 (20.5%)</td>
<td>90 (11%)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>31 (3.6%)</td>
<td>12 (1.5%)</td>
</tr>
<tr>
<td>Skin ischemia</td>
<td>56 (6.5%)</td>
<td>34 (4.1%)</td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>23 (2.7%)</td>
<td>20 (2.4%)</td>
</tr>
<tr>
<td>Refractory shock</td>
<td>196 (46%)</td>
<td>155 (41%)</td>
</tr>
</tbody>
</table>

Forest Plot By Type of Shock

- Hypovolemic
- Cardiogenic
- Septic
- All Patients

Hazard Ratio (95% CI)

- NE Better DA Better

Author’s Conclusions

- “Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events”

Discussion

- One of the largest studies to compare DA and NE head-to-head in shock syndromes
- 50% mortality rate consistent with norm
- High external validity including multiple forms of shock syndromes
- Early difference in cardiogenic shock mortality due to arrhythmias from dopamine

Limitations

- No mention of standard of care measures used or treatment of underlying cause
- ? Implemented similarly between groups
- Type of shock included
- Definition of “adequate administration of fluids” (1 L crystalloid, 500mL colloid)
- Definition of resolution of shock ill-defined
- Definition of “Equipotent” vasopressor dose
- Open-label NE allowed (26% DA & 20% NE)

Interpretation: Does NE no longer ‘leave ‘em dead’?

- Data challenges consensus guideline recommendation for dopamine as 1st-line
- Minimizes perception that norepinephrine causes excessive harmful organ vasoconstriction
- Implications for treatment of cardiogenic shock
- Guideline change may be warranted
- Consistent with SOAP 1 study
- Implications for procurement & administration