Updates in Therapeutics® 2012:

The Pharmacotherapy Preparatory Review & Recertification Course
Oncology Supportive Care
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Conflict of Interest Disclosures

LeAnn B. Norris – has no conflicts of interest to disclose

Learning Objectives

1. Identify, assess, and recommend appropriate pharmacotherapy for managing common complications of cancer chemotherapy, including nausea and vomiting; myelosuppression and the appropriate use of growth factors; infection; anemia and fatigue; cardiotoxicity; and extravasation injury.
2. Assess and recommend appropriate pharmacotherapy for managing cancer-related pain.
3. Assess and recommend appropriate pharmacotherapy for managing oncologic emergencies, including hypercalcemia, hyperuricemia, and spinal cord compression.

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Patient Case # 1

A 60-year-old woman was recently given a diagnosis of advanced non–small cell lung cancer. She is going to begin treatment with cisplatin 100 mg/m2 plus vinorelbine 30 mg/m2. Which one of the following is an appropriate antiemetic regimen for preventing acute emesis?

A. Aprepitant plus ondansetron plus dexamethasone.

B. Aprepitant plus prochlorperazine plus dexamethasone.

C. Aprepitant plus granisetron plus ondansetron.

D. Lorazepam plus ondansetron plus metoclopramide.

Handout Page 2-11; Answer Page 2-27

Definitions of Nausea/Vomiting

- Nausea: the inclination to vomit, a felling in the throat or epigastric region alerting an individual that vomiting is imminent.
- Vomiting: the ejection or expulsion of gastric contents through the mouth.
- Retching: the labored movement of abdominal and thoracic muscles before vomiting.

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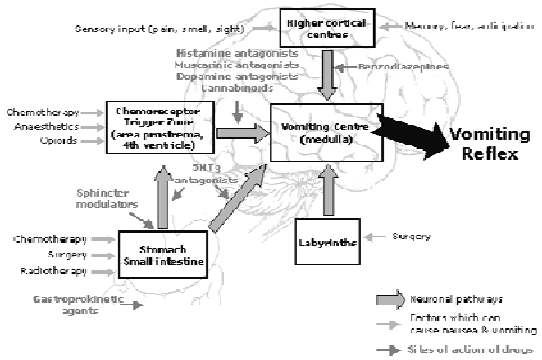
Definitions of Nausea/Vomiting

- Acute: 18-24 hours after chemotherapy.
- Delayed: > 18-24 hours after chemotherapy.
- Anticipatory: triggered by sight, smell or sounds due to inadequate control of nausea/vomiting in past
- Breakthrough: emesis that occurs the day of chemotherapy despite appropriate prophylaxis.
- Refractory: occurs during treatment cycles when antiemetic prophylaxis and/or rescue therapy have failed in previous cycles

Page2-11 (Answer pg2- 27)



Page 2-11 (Answer pg 2-27)

Risk Factors for Nausea/Vomiting

- Patient's age (younger patients or those < 50 years old)
- Female Gender
- History of motion sickness
- History of nausea or vomiting during pregnancy
- Poor control of nausea or vomiting in previous chemotherapy cycles
- History of chronic alcoholism (positive risk factor – decreases incidence of emesis)
- Emetegenicty of chemotherapy regimen

Page 2-11 (Answer pg2- 27)

Emetogenicity of Chemotherapy Regimen

- Several schemes for assessing emetogenicity have been proposed.
  - Originally, emetogenic risk was based as "none," "mild," "moderate," and "severe"
  - Hesketh model – proposed in 1997
  - Current model includes four levels for IV chemotherapy and 2 levels for oral chemotherapy
  - Levels for IV chemotherapy (e.g., minimal, low, moderate, high emetogenic risk) are defined by the percentage of patients expected to experience emesis
  - Levels for oral chemotherapy (prophylaxis recommended and PRN recommended)

Page 2- 11 (Answer pg 2-27)

Considerations for Antiemetic Selection:

- Patient factors: female gender
- Emetogenicity of chemotherapy: cisplatin is the most highly emetogenic chemotherapeutic agent.
- "Potency" and mechanism of antiemetic agents: prochlorperazine is NOT for highly emetogenic chemotherapy; lorazepam is useful for minimizing anticipatory symptoms; aprepitant for highly emetogenic chemotherapy and regimens causing delayed symptoms

Page 2-11 (Answer pg 2-27)

Considerations for Antiemetic Selection:

- Dexamethasone improves antiemetic activity by 10-20%
- Low dose metoclopramide has activity similar to phenothiazines; higher dose block serotonin receptors
- Metoclopramide is useful for preventing/treating delayed symptoms
- Answer A: aprepitant + ondansetron + dexamethasone

Page 2-11 (Answer pg 2-27)

Patient Case # 2

Which one of the following is an appropriate regimen for anticipatory nausea and vomiting?

A. Aprepitant plus dexamethasone.

B. Aprepitant plus metoclopramide..

C. Ondansetron plus dexamethasone.

D. Aprepitant plus ondansetron plus dexamethasone plus lorazepam

Handout Page 2-11; Answer Page 2-27

Anticipatory Nausea/Vomiting

- Anticipatory: triggered by sight, smell or sounds due to inadequate control of nausea/vomiting in past
- Serotonin receptor antagonists are generally not thought to be effective for anticipatory symptoms
  - Ondansetron plus dexamethasone – not a great option
- Aprepitant plus dexamethasone is a great option for delayed nausea/vomiting, but not anticipatory symptoms
- Aprepitant plus metoclopramide – not for anticipatory

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Considerations for Anticipatory Nausea/Vomiting

- Benzodiazepines (lorazepam)
  - Minimal antiemetic activity as single agent
  - Useful in combination with or as an adjunct to other antiemetics.
  - Anterograde amnesia helps prevent anticipatory nausea and vomiting.
  - Relief of anxiety
  - Management of akathisia caused by phenothiazines, butyrophenones, or metoclopramide

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Considerations for Anticipatory Nausea/Vomiting

- Benzodiazepines (lorazepam)
  - Adverse events:
    - Amnesia,
    - Sedation
    - Hypotension
    - Perceptual disturbances
    - Note that amnesia and sedation may, in fact, be desirable
- Answer D: Aprepitant+ ondansetron +dexamethasone+ lorazepam

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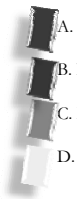
Patient Case # 3

A 75-year-old man has metastatic prostate cancer; his main sites of metastatic disease are regional lymph nodes and bone (several hip lesions). He has aching pain with occasional shooting pains. The latter are thought to be the result of nerve compression by enlarged lymph nodes. He has been taking oxycodone-APAP 5 mg 2 tablets every 4 hours and ibuprofen 400 mg every 8 hours. His current pain rating is 8/10, and he states that his pain cannot be controlled. Which one of the following choices is best to manage his pain at this time?



A. Increase oxycodone-APAP to 7.5 mg, 2 tablets every 4 hours.

B. Increase oxycodone-APAP to 10 mg, 2 tablets every 4 hours.

C. Discontinue ibuprofen and add morphine SR every 12 hours.

D. Discontinue oxycodone-APAP and add morphine every 12 hours.

Handout Page 2-15; Answer Page 2-27

Considerations for Pain Selection

- Severity of pain, as determined by the patient: "8" on a scale of 0 to 10 is "severe"
- Select a drug and dose to match the severity of pain
- Consider the limitations of combination products containing APAP, aspirin, etc.: strong opioids in combination products are used more like weak opioids

Page 2-15 (Answer pg 2-27)

Considerations for Pain Selection

- For persistent, severe pain, agents with a long duration of action are more convenient
- NSAIDs may be useful for bone pain; they do not replace opioids
- Answer D: Discontinue oxycodone/APAP and add morphine SR every 12 hours

Page 2-15 (Answer pg 2-27)

Patient Case # 4

Which one of the following might be an additional change in this patient's pain regimen?

- A. Naproxen.
- B. Single-agent (single ingredient) APAP.
- C. Gabapentin.
- D. Baclofen.

Handout Page 2-15; Answer Page 2-27

Considerations for Pain Management

- Adjuvant analgesics are drugs whose primary indication is other than pain relief
- Adjuvant analgesics are added to opioid regimens for specific pain syndromes
- NSAIDs for bone pain: pain from bone metastases is a common cause of pain in cancer

Page 2-15 (Answer pg 2-27)

Considerations for Pain Management

- Antidepressants and anticonvulsants are useful for neuropathic pain. Opioids are less effective in neuropathic as compared to nociceptive pain.
- Neuropathic pain occurs when tumor infiltrates nerves, or as a result of nerve compression by tumor
- Neuropathic pain is characterized by sharp, shooting, lancinating sensations, and dysesthesia
- Answer C: gabapentin

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Patient Case # 5

A 50-year-old woman is receiving adjuvant chemotherapy for stage II breast cancer. She received her third cycle of doxorubicin and cyclophosphamide (AC) 10 days ago. Her CBC today includes WBC 600/mm3,segmented neutrophils 60%, band neutrophils 10%, monocytes 12%, basophils 8%, and eosinophils 10%. Which one of the following best represents this patient's ANC?

- A. 600/mm^3.
- B. 360/mm^3.
- C. 240/mm^3.
- D. 420/mm^3.

Handout Page 2-18; Answer Page 2-27

Considerations for Neutropenia

- The ANC is the number of neutrophils + bands
- The importance of knowing the ANC is in predicting the risk of infection: ANC $\leq$ 500/mm^3 is considered neutropenic. The risk of infection increases as ANC drops below 1500/mm^3; risk increases with the duration of neutropenia
- The ANC in this patient is 420/mm^3
  - 600/mm^3 x (0.6 + 0.1) = 420/mm^3
- Answer D: 420/mm^3

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Patient Case # 6

Based on this ANC, which one of the following statements is most correct?

- A. The patient should be initiated on a CSF.
- B. The patient should begin prophylactic treatment with either a quinolone antibiotic or trimethoprim-sulfamethoxazole.
- C. The patient, who is neutropenic, should be monitored closely for signs and symptoms of infection.
- D. Decrease the doses of doxorubicin and cyclophosphamide with the next cycle of treatment.

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Considerations for the use of Colony Stimulating Factors(CSFs)

- CSFs are generally used to prevent neutropenia, as opposed to treating established neutropenia
  - Does the patient have a fever?
- Treatment of established febrile neutropenia should be considered when the patient is at risk for complications from infection
- The nadir ANC for most chemotherapy occurs at 7-10 days, followed by recovery of ANC

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Considerations for the use of Colony Stimulating Factors(CSFs)

- If subsequent chemotherapy is delayed due to low ANC, a CSF should be given after the next cycle (curative chemotherapy); alternatively the subsequent doses of chemotherapy can be decreased (non-curative chemotherapy)
- Prophylactic antibiotics is not recommended in this setting
  - Solid tumor patient
  - Afebrile
- Answer C: The patient, who is neutropenic, should be monitored closely for signs and symptoms of infection.

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Patient Case # 7

A 45-year-old woman is beginning her third cycle of chemotherapy for the adjuvant treatment of breast cancer. At diagnosis, her hemoglobin was 10 g/dL; however, today, her hemoglobin is less than 10 g/dL. The patient is experiencing considerable fatigue that is interfering with her activities of daily living. Which one of the following statements is true?

A. Treatment with epoetin should be considered.

B. Treatment with darbepoetin should be considered when hemoglobin falls to less than 9 g/dL.

C. Patient is being treated in the curative setting and therefore is not eligible to receive an ESA.

D. The patient should not receive RBC transfusions because she is symptomatic.

Handout Page 2-20; Answer Page 2-27

Considerations for Anemia and Fatigue

- Fatigue in cancer patients has multiple causes, one of which may be anemia
- Fatigue represents more than "feeling tired" and can compromise quality of life
- Attempts to increase Hgb with erythropoiesis-stimulating agents (ESAs) have been associated with decreased survival in some cancer patients

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Considerations for Anemia and Fatigue

- The use of ESAs should be limited to patients whose
  - Hgb is < 10 g/dL, and patients with chemotherapy-associated anemia (as opposed to cancer-associated anemia)
  - Only use in patients with non-curable cancer
- Transfusion is also an option for increasing Hgb
  - Goal 8 – 10 g/dL

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Considerations for Anemia and Fatigue

- Because she is being treated for breast cancer in the adjuvant setting, ESAs would not be appropriate.
- If this was a patient with advanced breast cancer or lung cancer, then these agents would be an option.
- Answer C: Patient is being treated in the curative setting and therefore is not eligible to receive an ESA.

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Patient Case # 8

A 38-year-old woman has a history of Hodgkin lymphoma. Two years ago, she completed six cycles of ABVD chemotherapy (i.e., doxorubicin, bleomycin, vinblastine, and dacarbazine). Each cycle included doxorubicin 50 mg/m2. Recently, she was given a diagnosis of stage IV breast cancer. She will be initiated on doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 for four cycles. Which one of the following statements is most applicable?

A. The patient has not reached the appropriate cumulative dose of doxorubicin to consider dexrazoxane.
B. The patient has reached the appropriate cumulative dose of doxorubicin to consider dexrazoxane.
C. The patient should not receive any more doxorubicin because she is at an increased risk of cardiotoxicity.
D. The patient should not receive dexrazoxane because of the possibility of increased myelosuppression.

Handout Page 2-22; Answer Page 2-27

Considerations for Dexrazoxane

- Consider the total cumulative dose (per BSA) of doxorubicin: 300 mg/m^2
- Consider the goal of therapy: palliative for metastatic disease; an early study suggested a decreased response rate to doxorubicin when dexrazoxane was used to prevent cardiac toxicity
- Dexrazoxane may add to the hematologic toxicity of chemotherapy

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Considerations for Dexrazoxane

- Dexrazoxane may be considered for patients with metastatic breast cancer who have received a cumulative dose of doxorubicin of $\geq$ 300 mg/m^2, and who may benefit from further drug
- This patient has received a cumulative doxorubicin dose sufficient to consider the use of dexrazoxane
- Answer B: The patient has reached the appropriate cumulative dose of doxorubicin to consider dexrazoxane.

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Patient Case # 9

Which one of the following is the correct sequence for administering mesna and ifosfamide?

A. Mesna before ifosfamide and then at 4 and 8 hours after ifosfamide.
B. Ifosfamide before mesna and then at 4 and 8 hours after mesna.
C. Mesna and ifosfamide beginning and ending at the same time.
D. Mesna on day 1 and ifosfamide on days 2–5.

Handout Page 2-22; Answer Page 2-27

Considerations for Mesna

- Mesna is a chemoprotectant that binds to acrolein to prevent the the binding of acrolein to the bladder and therefore causing sterile hemorrhagic cystitis
- Mesna is always used with ifosfamide, and may be used with cyclophosphamide
- Acrolein is a metabolite of both ifosfamide and cyclophosphamide that accumulates in the bladder. For chemoprotection, mesna must be available in the bladder when acrolein is present in the bladder.

Page 2-22 (Answer pg 2-27)

Considerations for Mesna

- When bolus doses of mesna and ifosfamide are used, mesna should be given before ifosfamide, then 4 hours and 8 hours after ifosfamide
- Answer A: Mesna before ifosfamide and then at 4 and 8 hours after ifosfamide.

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Patient Case # 10

A 40-year-old man is about to begin R-CHOP chemotherapy for large cell non Hodgkin lymphoma. The patient asks how long the treatment will take and whether he can be treated as an outpatient. Which one of the following is the best answer?

A. Administration of this regimen is expected to be complete in 1 hour, but because the regimen is highly emetogenic, it is usually given to patients while in the hospital.

B. Administration of this regimen may take as long as 6 hours because the rituximab infusion rate is slowly increased, but the regimen is usually given to outpatients.

C. Administration of this regimen may take as long as 6 hours because the vesicants doxorubicin and vincristine should be infused over several hours, but the regimen is usually given to outpatients.

D. Administration of this regimen is expected to be complete in 1 hour, but because of the risk of tumor lysis syndrome, it is usually given to patients in the hospital.

Handout Page 2-24; Answer Page 2-27

Considerations for Administration of Chemotherapy

- In the CHOP-R regimen, cyclophosphamide, doxorubicin and vincristine can all be given as bolus injections or short infusions. Prednisone is given orally.
- Both doxorubicin and vincristine are vesicants, and it is generally preferred to give vesicants as bolus injections. Vincristine is often given as a short infusion to avoid inadvertent intrathecal administration.
- Rituximab and other chimeric antibodies are associated with infusion reactions. Thus the rate of administration of rituximab is usually titrated slowly

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Considerations for Administration of Chemotherapy

- Highly emetogenic chemotherapy is commonly given in the outpatient setting, with appropriate antiemetic prophylaxis.
- Tumor lysis syndrome occurs subsequent to cell death in tumors that are rapidly growing and highly chemosensitive.
- Large cell lymphoma is considered intermediate in terms of risk of developing TLS, and is commonly treated in the outpatient setting.

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Considerations for Administration of Chemotherapy

- In this patient, administration of CHOP-R may take as long as 6 hours because the rituximab infusion rate is slowly increased. But the CHOP-R regimen is usually given to outpatients.
- Answer B: Administration of this regimen may take as long as 6 hours because the rituximab infusion rate is slowly increased, but the regimen is usually given to outpatients.

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Updates in Therapeutics® 2012:

The Pharmacotherapy Preparatory Review & Recertification Course
Men's and Women's Health

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Conflict of Interest Disclosures

Erin C. Raney, Pharm.D., BCPS
- No conflicts of interest
- Nothing to disclose for this presentation

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Learning Objectives

1. Recommend appropriate treatment options for patients with menopausal symptoms, osteoporosis, and sexual dysfunction.
2. Identify drugs that are considered safe and unsafe in pregnancy and lactation.
3. Modify contraceptive regimens based on estrogen- and progestin-related adverse effects or drug interactions.
4. Devise a pharmacotherapeutic plan for appropriate contraceptive use, misused contraceptive methods, and use of emergency contraception.
5. Identify the common sexually transmitted diseases and recommend appropriate pharmacotherapy.

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Agenda

- Menopause
- Osteoporosis
- Pregnancy and Lactation
- Contraception
- Sexually Transmitted Infections
- Sexual Dysfunction in Men
- Infertility*

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Menopause

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Patient Case A

N.I. is a 51-year-old woman with hot flashes and vaginal irritation. Has tried exercise, diet, and antidepressants and is unsuccessful. Otherwise healthy with no history of cancer and no surgeries. States hot flashes are interfering with her daily activities and wants to try hormone therapy.

1. Which one of the following was proved statistically significant with conjugated estrogens and medroxyprogesterone acetate and should be mentioned to N.I.?

A. Decreased risk of stroke.
B. Decreased risk of MI.
C. Increased risk of fractures.
D. Increased risk of DVT.

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Signs & Symptoms

Vasomotor
- Hot flashes/flushes*
- Night sweats*

Psychological
- Anxiety
- Depression
- Insomnia
- Mood Swings

Vaginal Dryness
- Genitourinary atrophy*

Psychosomatic
- Pressure/tightness in head or body
- Headache
- Muscle/joint pain
- Numbness/tingling in feet/hands
- Dizzy or faint
- Difficulty breathing

***Directly related to estrogen deficiency**

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Common Hormone Regimens

- Unopposed estrogen
  - Only if no uterus due to increased risk of endometrial cancer
- Estrogen plus cyclic progestogen (progestin)
- Estrogen plus daily (continuous) progestogen
  - Heart and Estrogen/Progestin Replacement Study (HERS)
    - JAMA. 1998;280:605-13
  - **Women's Health Initiative (WHI)**
    - JAMA. 2002;288:321-33
- Intermittent estrogen plus progestogen

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Summary of Findings (WHI)

Risk or Benefit	Relative Risk	Absolute Risk each Year
Heart attacks	1.29 or 29% ↑	7 more cases in 10,000 women
Breast Cancer	1.26 or 26% ↑	8 more cases in 10,000 women
Strokes	1.41 or 41% ↑	8 more cases in 10,000 women
Blood clots	2.11 or 111% ↑	18 more cases in 10,000 women
Hip fractures	0.66 or 33% ↓	5 fewer cases in 10,000 women
Colon Cancer	0.63 or 37% ↓	6 fewer cases in 10,000 women
Dementia*	2.05 or 105% ↑	23 more cases in 10,000 women over 65

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Patient Case A

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A. Decreased risk of strokes.
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C. Increased risk of fractures.
D. Increased risk of DVT.

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Updated References

- The 2012 Hormone Therapy Position Statement of The North American Menopause Society (NAMS)
  - Menopause 2012;19(3):257-71.
  - Available at http://www.menopause.org/psht12.pdf

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Recommendations – NAMS 2012

- Moderate to severe vasomotor symptoms:
  - Primary indication for HT
  - Recommend lowest effective dose
- Moderate to severe vaginal symptoms:
  - Recommend local ET vs. systemic therapy if treating vaginal symptoms only
- Sexual function:
  - HT not recommended for sole treatment of diminished libido
- Urinary health:
  - Systemic HT may worsen stress incontinence, local ET therapy may help with overactive bladder
- Osteoporosis:
  - HT indication for prevention, ↓osteoporotic fractures, used only when alternate therapies are not appropriate

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Recommendations – NAMS 2012

- Risks
  - Venous thromboembolism
  - CVD
    - Risk appears higher when HT initiated further from onset of menopause
  - Breast cancer
    - Estrogen combined with progestogen appears to have risk with 4-5 years of use
    - Estrogen alone has different risk profile (appears later)
  - Cognitive function
  - Additional data needed
    - Ovarian cancer
    - Lung cancer

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Alternatives for Vasomotor Symptoms

- Serotonin reuptake inhibitors
  - Fluoxetine (Prozac®)
  - Paroxetine (Paxil®)
  - Sertraline (Zoloft®)
  - Venlafaxine (Effexor®)
- Others
  - Clonidine
  - Megestrol
  - Gabapentin
  - Natural products

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Patient Case A

N.I. is a 51-year-old woman with hot flashes and vaginal irritation. Has tried exercise, diet, and antidepressants and is unsuccessful. Otherwise healthy with no history of cancer and no surgeries. States hot flashes are interfering with her daily activities and wants to try hormone therapy.

2. Which one of the following HT treatments should be recommended to N.I.?

A. Alora® patch (17-ß-estradiol) 0.025 mg; change patch twice weekly
B. Climara® patch (17-ß-estradiol) 0.025 mg; change patch once weekly
C. Prempro® (conjugated estrogens/ medroxyprogesterone acetate); 0.3 mg/1.5 mg; take 1 tablet daily
D. Premarin® (conjugated estrogens) 0.625 mg; take 1 tablet daily

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Osteoporosis

Patient Case B

C.A. is a 71-year-old white woman with a history of rheumatoid arthritis who smokes ½ pack/day. She takes calcium 500 mg /vitamin D 400 IU 3 times/day. She is 5′3″ and weighs 140 lbs. Her BMD T-score is −2.5 at the hip and −2.1 at the spine. Her FRAX score is 10-year major fracture risk of 22% and 10-year hip fracture risk of 9.6%.

3. Which one of the following statements best describes the correct diagnosis for C.A.?

A. Normal BMD of the spine.
B. Osteopenia of the spine.
C. Osteoporosis of the spine.
D. Osteoporosis is defined when a fracture has occurred.

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Osteoporosis Definitions

World Health Organization Definitions

- **Normal** = BMD within 1 standard deviation (SD) of the young adult mean
- **Osteopenia** = BMD between −1 SD and −2.5 SD below the young adult mean
- **Osteoporosis** = BMD at least −2.5 SD

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References

- 2008 National Osteoporosis Foundation Clinician's Guide to Prevention and Treatment of Osteoporosis
  - Available at http://www.nof.org/professionals/clinical-guidelines (updated on-line)
- 2010 North American Menopause Society Position Statement on the Management of Osteoporosis in Postmenopausal Women
  - Menopause. 2010;17(1):25-54.
  - Available at http://www.menopause.org/PSosteo10.pdf
- 2010 AACE Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis
  - Endocrine Practice. 2010;16(Suppl 3):1-37.
  - Available at http://www.aace.com

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Risk Factors

- Female
- White race
- Poor nutrition, long-term low-calorie intake
- Early menopause (before age 45) or prolonged amenorrhea
- Estrogen deficiency
- Drugs:
  - Glucocorticoids
  - Heparin
  - Anticonvulsants
  - Excessive levothyroxine
  - GnRH agonists
  - Lithium
  - Cancer drugs
- Low body mass index (BMI) or low weight
- Family history of osteoporosis
- Low calcium and vitamin D intake
- Sedentary lifestyle, decreased mobility
- Cigarette smoking
- Alcoholism
- Dementia
- Impaired eyesight despite adequate correction
- Previous fractures
- History of falls

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Risk Assessment

- FRAX® Score – platform created to calculate 10-year fracture risk
  - Available at http://www.shef.ac.uk/FRAX/ or http://www.nof.org
  - Includes 10 risk factors: age, sex, weight, height, femoral neck BMD, parental history of fractures, tobacco use, glucocorticoids, rheumatoid arthritis, alcohol use, other secondary causes
- Bone mineral density (BMD) testing
  - Dual-energy x-ray absorptiometry (DXA)- gold standard

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Screening Recommendations

- BMD Measurements
  - All women 65 years and older
  - Postmenopausal women with medical causes of bone loss (hyperparathyroidism, steroid use, etc.)
  - Postmenopausal women age 50 and older with risk factors: fracture after menopause, wt <127 lbs or BMI <21 kg/m^2, smoker, parent w/ hip fracture, rheumatoid arthritis, alcohol > 2 units/day
  - Postmenopausal women with fragility fracture
  - All men older than 70 years of age
  - Men ages 50-70 with risk factors or previous fractures

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Patient Case B

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3. Which one of the following statements best describes the correct diagnosis for C.A.?

A. Normal BMD of the spine.
B. Osteopenia of the spine.
C. Osteoporosis of the spine.
D. Osteoporosis is defined when a fracture has occurred.

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Lifestyle Modifications

Recommendations

- Advise patient to avoid smoking and to consume only moderate amounts of alcohol.
- Encourage regular weight-bearing and muscle-strengthening exercise.
- Encourage adequate intake of calcium (at least 1000 mg/day) and vitamin D (600–800 IU/day). For older than 70 years – 800 IU/day.
- Assess fall risks.

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Initiating Pharmacotherapy

- Based on NOF, AACE, and NAMS recommendations:
  - Hip or spine fracture
  - T-score -2.5 or below at hip, spine, or femoral neck
  - T-score between -1.0 and -2.5 with a 10-year probability of a hip fracture ≥ 3% **OR** a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the FRAX® tool (US-adapted WHO algorithm)

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Current Treatments

- Bisphosphonates (1st line)
- Selective estrogen receptor modulators (SERMs)
- Calcitonin
- Teriparatide
- Denosumab
- Hormone therapy

Pages 2-42 to 2-45

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Bisphosphonates

- Inhibit osteoclasts, reduce bone resorption
- Reduce risk of vertebral fractures by 40-70%
- Reduce risk of non-vertebral fractures (hip) by 20-35%
- Adverse effects: Oral agents → most common is esophageal/gastric irritation
- Must be taken on an empty stomach and remain upright for at least 30 min. (60 min for ibandronate)
- Only use in patients with GFR of > 30mL/min (see individual agents)
- Additional risks: osteonecrosis of jaw, atypical fractures

Pages 2-42, 2-43

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Bisphosphonates

- Alendronate (Fosamax®) PO daily or weekly
- Risedronate (Actonel®) PO daily, weekly, monthly
- Risedronate (Atelvia®) PO weekly (delayed release, take 30 min. after breakfast, avoid PPI use)
- Ibandronate (Boniva®) PO daily, monthly or IV Q 3 months
- Zolendronic acid (Reclast®) IV yearly or Q 2 years for prevention
- Etidronate (approved in Canada for osteoporosis)

Pages 2-42, 2-43

69

SERMS (Selective Estrogen Receptor Modulators)

- Raloxifene (Evista®) 60 mg PO daily
  - Approved for prevention and treatment of osteoporosis
  - Adverse effects: increased VTE events, may cause hot flashes or leg cramps
- Calcitonin (Miacalcin®) 200 IU daily intranasally
  - Approved for treatment, usually alternative if other agents cannot be used
  - Effective for reducing risk of vertebral fractures only, may help with bone pain from compression fractures
  - Adverse effects (nasal): rhinitis, epistaxis

Page 2-44

70

Other Therapies

- Teriparatide (Forteo®): recombinant human PTH
  - Subcutaneous injection 20 mcg/day for up to 24 months
  - Rare risk of osteosarcoma (seen in animal studies)
- Denosumab (Prolia®)
  - Inhibits osteoclast-mediated bone resorption, monoclonal antibody binds to RANKL
  - Subcutaneous injection (60 mcg) every 6 months
  - Safety issues: infections, hypocalcemia
- Hormone therapy
  - Approved for prevention only

Page 2-45

71

Patient Case B

C.A. is a 71-year-old white woman with a history of rheumatoid arthritis who smokes ½ pack/day. She takes calcium 500 mg /vitamin D 400 IU 3 times/day. She is 5′3″ and weighs 140 lbs. Her BMD T-score is −2.5 at the hip and −2.1 at the spine. Her FRAX score is 10-year major fracture risk of 22% and 10-year hip fracture risk of 9.6%.

4. Which one of the following is the best therapy for C.A.?

A. Teriparatide 20 mcg SQ daily.

B. Alendronate 70 mg PO every week.

C. Miacalcin nasal spray 1 spray (200 IU) in one nostril daily.

D. No additional therapy required, continue on calcium and vitamin D.

Page 2-42, Answer Page 2-86

72

Pregnancy and Lactation

Patient Case C

S.E. is a 28-year-old woman who would like to get pregnant soon. Her medical history includes hypertension and seasonal allergies. Her medications include lisinopril, nasal saline spray, and folic acid.

5. Which one of the following is best to treat her hypertension while she is pregnant or trying to conceive?

A. Continue lisinopril.
B. Discontinue lisinopril and all other medications.
C. Discontinue lisinopril and start methyldopa.
D. Continue lisinopril and add metoprolol.

Page 2-49

74

Drug Use in Pregnancy

- General approaches
  - Assess current drug use if trying to conceive.
  - Folic acid (at least 400 mcg daily) prior to conception to prevent neural tube defects.
  - Teratogen: drug or environmental agent that has potential to cause abnormal fetal growth and development.
  - Consider trimester and timing of medication administration.
  - Assess drug safety versus benefit.

Pages 2-46, 2-47

75

FDA Pregnancy Risk Classifications

- Summary (See Table 9, page 2-46):
  - A: Controlled studies show no risk
  - B: No evidence of risk in humans
  - C: Risk cannot be ruled out (no studies in humans)
  - D: Positive evidence of risk
  - X: Contraindicated in pregnancy, definite risk
- New labeling recommended by FDA

Pages 2-46, 2-47

76

Known Teratogens

- Isotretinoin
- Methotrexate
- Alcohol
- Mercury
- Thalidomide
- Androgens
- Cocaine
- Tetracycline
- Vitamin A
- Statins
- ACE inhibitors
- Diethylstilbestrol
- Warfarin
- Lead
- Carbamazepine
- Topiramate
- Phenytoin
- Valproate
- Lithium

Page 2-47

77

Conditions in Pregnancy– Key Concepts

- GI (nausea and vomiting)
  - Options include antihistamines, ondansetron, metoclopramide
- Headache
  - Acetaminophen recommended first-line
  - Avoid use of NSAIDs, ASA (consider trimester), triptans, ergot derivatives
- Coagulation disorders
  - Heparin/LMWH preferred for anticoagulation; AVOID warfarin
- Diabetes
  - Insulin preferred; sulfonylureas/metformin studied
- Hypertension
  - AVOID ACE inhibitors/ARBs; methyldopa is first-line (can also use certain beta-blockers, CCBs)

Pages 2-49 to 2-51

78

Patient Case C

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5. Which one of the following is best to treat her hypertension while she is pregnant or trying to conceive?

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D. Continue lisinopril and add metoprolol.

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79

Drug Use in Lactation

- Consider risk vs. benefit
- Pump and discard milk
- Choose drugs with shorter half-lives
- Drugs enter human milk if they are:
  - Highly lipid soluble
  - In high concentration in the mother's plasma
  - Low in molecular weight (<500)
  - Low in protein binding
  - Easily cross the blood-brain barrier

Pages 2-48, 2-49

80

Contraception

Patient Case D

Y.G. is a 33-year-old woman who was initiated on Mircette 4 months ago for contraception. She has breakthrough bleeding at the start of her active pills that lasts a few days before resolving. The physician wants to change the OC.

6. Which one of the following OCs on her formulary is the best for the physician to prescribe?

A. Continue on Mircette for another 3 months.
B. Change to Ortho-Cept.
C. Change to Loestrin 21.
D. Change to Lessina.

Page 2-55

82

Contraceptive Methods

- Combined hormonal contraceptives
  - Oral tablet
  - Patch
  - Vaginal ring
- Progestin-only
  - Oral tablet
  - Injection
  - Implant
  - Intrauterine system
- Non-hormonal

Page 2-54

83

Combined Contraceptives: Contraindications (Category 4)

- Less than 3-6 wks postpartum
- Smoker ≥ 35 yrs old
- Multiple risk factors for CVD
- BP >160/100
- Vascular disease
- Current or history of DVT/PE
- Complicated diabetes
- Presence of liver tumors, severe cirrhosis, or active viral hepatitis
- Major surgery with prolonged mobilization
- Known thrombogenic mutations
- Current or history of ischemic heart disease
- Stroke (history of CVA)
- Complicated valvular heart disease
- Migraine headache with aura or migraine without aura if
- Current breast cancer ≥ 35 yrs old

http://www.who.int/reproductive-health/publications/MEC_3/summary_tables.html

Pages 2-57

84

Combined Contraceptives: Side Effects

Estrogenic
- Nausea, vomiting
- Bloating, edema
- Irritability
- Cyclic weight gain
- Cyclic headache
- Hypertension
- Breast fullness, tenderness

Progestational and Androgenic**
- Headaches
- Increased appetite
- Increased weight gain
- Depression, fatigue
- Changes in libido
- Hair loss, hirsutism**
- Acne, oily skin**

Pages 2-56 to 2-58

85

Managing Side Effects

- Nausea
  - Usually related to estrogen content
  - Take at bedtime or with food
- Acne
  - Choose less androgenic formulation or higher estrogen activity
- Breakthrough bleeding and spotting
  - If unexpected bleeding occurs, use additional contraception until bleeding completely ceases
  - Rule out potential causes (e.g., pelvic inflammatory disease)
  - Encourage continuation if first few cycles

Pages 2-57, 2-58

86

Managing Side Effects

- Breakthrough bleeding and spotting (cont'd)
  - When switch is indicated:
    - Increase estrogen dose
      - If bleeding begins during first 14 days
      - If absence of withdrawal menses
      - If menses continues into active pill cycle
    - Change progestin
      - If bleeding begins after 14 days (late in the cycle)
      - Progestin should have higher progestational and/or androgenic activity
    - Increase both estrogen and progestin
      - If bleeding occurs midcycle

Page 2-57, 2-58

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Patient Case D

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C. Change to Loestrin 21.
D. Change to Lessina.

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Patient Case D

Name of OC	Estrogen Property	Progestin property	Androgen property
Mircette (desogestrel 0.15mg /EE 20mcg)	Low	High	Low
Ortho-Cept (desogestrel 0.15mg /EE 30 mcg)	Intermediate	High	Low
Lessina (levonorgestrel 0.1mg/EE 20mcg)	Low	Low	Low
Loestrin 21 (norethindrone acetate 1.5 mg/ 30 mcg)	Low	High	High

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Patient Case D

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6. Which one of the following OCs on her formulary is the best for the physician to prescribe?

A. Continue on Mircette for another 3 months.
B. Change to Ortho-Cept.
C. Change to Loestrin 21.
D. Change to Lessina.

Page 2-55, Answer Page 2-86

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Combined Contraceptives: Drug Interactions

- Common hepatic enzyme inducers (may reduce contraceptive effectiveness)
  - Rifampin - significant risk of failure
  - Anticonvulsant agents most likely to cause breakdown of estrogen or progestin: phenobarbital, phenytoin, topiramate, carbamazepine, primidone
  - St. John's wort
  - Management
    - Use another contraceptive method
    - Use different therapeutic agent (i.e. anticonvulsant)
    - Use contraceptive with higher estrogen doses

Pages 2-58, 2-59

91

Combined Contraceptives: Drug Interactions

- Drospirenone
  - Interacts with NSAIDs, ACE Inhibitors, increases serum potassium levels
- Antibiotics (broad-spectrum)
  - Reported cases in the literature of contraceptive failure; not possible to identify women who may be at risk of OC failure.
  - Recent WHO/CDC eligibility criteria do not recommend alternate contraception.
  - Counsel about the additional use of nonhormonal contraception or alternate methods:
  - Those not comfortable with risk of interaction
  - Those with previous failures or who develop breakthrough bleeding during use of antibiotics

Pages 2-58, 2-59

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Combined Contraceptives

- Extended regimens
  - 3 month formulations
  - 1 year formulations
  - Breakthrough bleeding common
- Unique oral formulations (select examples)
  - Quadriphasic
    - Natazia® (estradiol valerate/dienogest)
  - Contain levomefolate calcium
    - Safyral® (ethinyl estradiol 30 mcg /drospirenone 3 mg)
    - Beyaz® (ethinyl estradiol 20 mcg /drospirenone 3 mg)
  - Low estrogen
    - Lo Loestrin Fe® (ethinyl estradiol 10 mcg/ norethindrone acetate 1 mg)

Pages 2-60, 2-61

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Patient Case E

L.M. is a 37-year-old woman, going to get married, needs birth control pills for now, wants children in a year. PMH: hypertension x 2 years, GERD, admits to 2 glasses of wine/week and smokes ½ pack per day. Meds: HCTZ 25 mg PO daily, Lotrel 5/20 (amlodipine/benazepril) PO daily, Prilosec 20 mg (omeprazole) PO daily, and occasional ibuprofen. She is 5'7", Weight: 210 lbs. (95kg).

7. Which one of the following contraceptive products is best to recommend for L.M.?

A. Transdermal contraceptive patch
B. Oral tablet ethinyl estradiol/drospirenone
C. Oral tablet norethindrone
D. Depot medroxyprogesterone acetate injection

Page 2-68

94

Combined Contraceptives

- Non-oral
  - Transdermal patch (Ortho-Evra®)
    - Increased exposure to estrogen, 60% more estrogen than in women taking 35 mcg of ethinyl estradiol
    - Increased risk of VTE, cardiovascular and cerebrovascular events?
    - Less effective in women > 198 lbs. (90kg)
  - Vaginal ring (NuvaRing®)
    - Insert vaginally and leave for 3 weeks, one week off, then repeat
    - Consider correct administration technique, specific recommendations for expulsion

Pages 2-62, 2-63

95

Progestin-Only Contraceptives

- Progestin-only "mini-pills" (POPs)
  - Take one pill at the SAME TIME daily until end of pack. Start next pack the next day.
  - More than a 3 hour delay is considered to be a "missed dose"
  - If a pill is missed, take missed pill(s) and use backup for 48 hours.

Pages 2-63, 2-64

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Progestin-Only Contraceptives

- Depot medroxyprogesterone acetate (Depo-Provera®, DMPA) injection
  - Injection administered every 11-13 weeks
  - Side effects
    - Weight gain
    - Mood issues, other progestin related effects
    - Long return to fertility
    - Possible decrease in BMD, especially in younger women with use > 5 years

Page 2-65

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Progestin-Only Contraceptives

- Levonorgestrel intrauterine system (Mirena®)
  - Releases 20 mcg/day of levonorgestrel
  - Effective for 5 years
  - Risks include infections and expulsion (patient counseling points)
  - Quick return to fertility
- Implantable rod (etonogestrel- Implanon/Nexplanon®)
  - Effective for 3 years
  - Insertion-site reactions
  - Concern with weight and effectiveness

Pages 2-65 to 2-67

98

Patient Case E

L.M. is a 37-year-old woman, going to get married, needs birth control pills for now, wants children in a year. PMH: hypertension x 2 years, GERD, admits to 2 glasses of wine/week and smokes ½ pack per day. Meds: HCTZ 25 mg PO daily, Lotrel 5/20 (amlodipine/benazepril) PO daily, Prilosec 20 mg (omeprazole) PO daily, and occasional ibuprofen. She is 5'7", Weight: 210 lbs. (95kg).

7. Which one of the following contraceptive products is best to recommend for L.M.?

A. Transdermal contraceptive patch

B. Oral tablet (ethinyl estradiol/drospirenone)

C. Oral tablet (norethindrone)

D. Depot medroxyprogesterone acetate injection

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Emergency Contraception

- Indications
  - Unprotected intercourse in the past 120 hours (OTC products labeled for use within 72 hours)
  - Contraceptive failure
    - Condom breaks
    - Missed oral contraceptive pills
    - Expulsion of IUD or vaginal ring
    - Patch fell off for long period of time
    - Displacement of barrier method (diaphragm)
  - Sexual assault
  - Exposure to teratogen

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Emergency Contraception

- Yuzpe Regimen – high dose estrogen + progestin
- Levonorgestrel – progestin only
  - Next Choice® (0.75 mg, 2 tablets in package), tablets may be taken 12 hours apart or together at one time.
  - Plan B One Step® (1.5 mg, 1 tablet taken as soon as possible after unprotected intercourse).
  - OTC for 17 years and older
- Ulipristal acetate – Selective Progesterone Receptor Modulator (SPRM)
  - Ella® 30 mg, 1 tablet taken as soon as possible after unprotected intercourse, labeled for use within 120 hours
  - Prescription-only
- Copper IUD
  - Use within 5 days of unprotected intercourse

Pages 2-68, 2-69

101

Sexually Transmitted Diseases/ Gynecologic Infections

Sexually Transmitted Infections/Diseases

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. MMWR 2010; 59: 1-110.
- Available at www.cdc.gov/std/treatment/

103

Herpes Simplex Virus (HSV)

- Therapy can help control symptoms but does not affect risk, frequency or severity of recurrences (50-80% recur)
- Virus remains latent in sacral dorsal root ganglia
- Initial HSV infection
  - Acyclovir 400 mg orally 3 times/day for 7–10 days
  - Acyclovir 200 mg orally 5 times/day for 7–10 days
  - Famciclovir 250 mg orally 3 times/day for 7–10 days
  - Valacyclovir 1 g orally 2 times/day for 7–10 days

Pages 2-73, 2-74

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HSV

- Recurrent HSV infection
  - If treatment is initiated within 1 day of lesion onset, patients with recurrent infections may benefit.
  - See page 2-74 for regimens of acyclovir, famciclovir, and valacyclovir
- Suppressive therapy
  - Recommended in patients with six or more episodes yearly (reassess annually the need for suppressive therapy)
    - Acyclovir 400 mg orally 2 times/day
    - Famciclovir 250 mg orally 2 times/day
    - Valacyclovir 500 mg/day orally
    - Valacyclovir 1000 mg/day orally

Page 2-74

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Patient Case F

D.H. is a 21 year old woman who presents with genital itching and vesicles on her vulva. She is sexually active with one partner who has a history of herpes. Her partner does not always use a condom. She is initiated on acyclovir for this initial herpes simplex infection.

9. Which of the following statements is best to mention to D.H. regarding treatment of her herpes infection?

A. Treatment will decrease the risk of recurrent herpes infections.
B. Treatment will shorten the duration of symptoms and infectivity of the initial infection.
C. Treatment will decrease the severity of recurrent herpes infections.
D. Treatment will prevent the virus from remaining latent in the dorsal root ganglia.

Page 2-74, Answer Pages 2-86, 2-87

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Patient Case F

10. D.H. returns to the clinic 10 months after her initial herpes infection. She is troubled by all of the recurrences she is having (seven to date). Which one of the following therapies is best to recommend?

A. Valacyclovir 500 mg orally 2 times/day to be used for 5 days whenever she notices a recurrence beginning.
B. Acyclovir 400 mg orally 3 times/day to be used for 10 days whenever she notices a recurrence beginning.
C. Suppressive therapy with famciclovir 250 mg orally 3 times/day.
D. Suppressive therapy with valacyclovir 500 mg/day orally.

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Sexually Transmitted Infections

- Syphilis (primary)- Benzathine penicillin G 50,000 units/kg up to 2.4 million units IM (adults), doxycycline 100 mg PO BID x 2 weeks
- Chlamydia – Azithromycin 1 gm in a single dose or doxycycline 100 mg 2 times/day for 7 days
- Gonorrhea – Ceftriaxone 250 mg IM **or** cefixime 400 mg orally—all as a single dose **PLUS** treatment of chlamydia if not ruled out
  - Fluoroquinolones no longer recommended because of resistance

Pages 2-75 to 2-77

108

Complications

- Urethritis
- Prostatitis
- Pelvic Inflammatory Disease (PID)

Pages 2-77 to 2-80

109

Patient Case G

M.A. is a 24-year-old woman with severe abdominal pain, fever, dysuria, and a vaginal discharge. She is sexually active with multiple partners. PMH unremarkable except for recurrent genital herpes (one or two episodes per year). Medications: oral contraceptive, fluticasone nasal spray as needed. Temp. 101.2°F (38°C), HR 92, RR 15, BP 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge.

11. Which one of the following is the best empiric therapy?

A. Ampicillin/sulbactam 2 g IV every 6 hours for 14 days.
B. Metronidazole 500 mg IV 3 times/day for 7 days.
C. Cefotetan 2 g IV every 12 hours with doxycycline 100 mg orally every 12 hours for 14 days.
D. Ceftriaxone 125 mg IM × 1 with doxycycline 100 mg IV 2 times/day for 7 days.

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110

Pelvic Inflammatory Disease

- Parenteral treatment:
  - Discontinued 24 hours after clinical improvement and switched to oral therapy for 14 days.
  - Regimen A: cefotetan 2 g intravenously every 12 hours or cefoxitin 2 g intravenously every 6 hours **PLUS** doxycycline 100 mg intravenously or orally every 12 hours
  - Regimen B: clindamycin 900 mg intravenously every 8 hours **PLUS** gentamicin intravenously/intramuscularly 2-mg/kg loading dose; then 1.5 mg/kg every 8 hours (or once-daily therapy)

Pages 2-77, 2-88

111

Pelvic Inflammatory Disease

- Alternative regimens:
  - Ampicillin-sulbactam 3 g intravenously every 6 hours plus doxycycline 100 mg intravenously **or** orally every 12 hours
  - Ceftriaxone 250 mg intramuscularly once (other third-generation cephalosporins also acceptable) or cefoxitin 2 g intramuscularly plus probenecid 1 g orally once **PLUS** doxycycline 100 mg 2 times/day for 14 days with or without metronidazole 500 mg orally 2 times/day for 14 days
- Sexual partners of patients with PID within the past 60 days should be tested and treated.

Pages 2-77, 2-88

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Patient Case G

M.A. is a 24-year-old woman with severe abdominal pain, fever, dysuria, and a vaginal discharge. She is sexually active with multiple partners. PMH unremarkable except for recurrent genital herpes (one or two episodes per year). Medications: oral contraceptive, fluticasone nasal spray as needed. Temp. 101.2°F (38°C), HR 92, RR 15, BP 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge.

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C. Cefotetan 2 g intravenously every 12 hours with doxycycline 100 mg orally every 12 hours for 14 days.
D. Ceftriaxone 125 mg intramuscularly × 1 with doxycycline 100 mg intravenously 2 times/day for 7 days.

Page 2-76, Answer Page 2-87

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Vaginal Infections

- Bacterial Vaginosis
  - Metronidazole or clindamycin
  - Malodorous vaginal discharge
  - Treatment of sexual partners is unnecessary
- Trichomoniasis
  - Metronidazole
  - Malodorous yellow-green vaginal discharge
  - **All sexual partners should be treated
- Vulvovaginal Candidiasis
  - OTC/Rx vaginal antifungals (1, 3, and 7 day regimens- see Table 23) and oral fluconazole
  - Intense itchiness and beige, milky vaginal discharge
  - Recurrent (4 or more episodes/year) may require longer treatment, maintenance therapy

Pages 2-78, 2-79

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Patient Case H

A 65-year-old man presents to his physician complaining of symptoms determined to be erectile dysfunction (ED). He has a history of hyperlipidemia, GERD, and glucose intolerance. His current medications include atorvastatin 20 mg PO daily, omeprazole 20 mg PO daily, and aspirin 81 mg as tolerated. He states that he heard of medications to help with his symptoms but does not want to have to plan out his intimate moments.

13. Which of the following drugs would work best for this patient?

A. Tadalafil
B. Vardenafil
C. Yohimbine
D. Bupropion

Page 2-82

115

Male Sexual Dysfunction

- Reduced libido from organic or psychological causes
  - Low serum testosterone concentrations
  - Increased concentrations of serum prolactin
- Ejaculation
  - Premature
  - Retarded
  - Absent
  - Retrograde
- Erectile dysfunction
  - Psychological
  - Organic
  - Mixed
  - Other causes (drugs)

Page 2-80

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Male Sexual Dysfunction

- Treat underlying cause, if possible
- Control risk factors
- Non-pharmacological: vacuum pump devices, venous constriction rings
- Pharmacological:
  - Testosterone replacements: injection, patch, gel, topical solution, buccal system, pellet
    - Specific application instructions
    - Avoid in patients with prostate cancer
    - Monitor for liver toxicity, increased lipids/BP, enlarged prostate
  - Yohimbine
  - Alprostadil injection or pellets

Pages 2-81, 2-82

117

Male Sexual Dysfunction

- Phosphodiesterase Type 5 Inhibitors:
  - Options
    - Sildenafil (Viagra®) 50 mg PO 1 hr. prior to intercourse
    - Tadalafil (Cialis®) 10 mg PO 36 hrs. prior (also daily administration 2.5-5 mg)
    - Vardenafil (Levitra®) 10 mg PO 1 hr prior to intercourse
  - Contraindicated with nitrate use, caution with cardiovascular disease

Pages 2-81, 2-82

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Patient Case H

A 65-year-old man presents to his physician complaining of symptoms determined to be erectile dysfunction (ED). He has a history of hyperlipidemia, GERD, and glucose intolerance. His current medications include atorvastatin 20 mg PO daily, omeprazole 20 mg PO daily, and aspirin 81 mg PO daily as tolerated. He states that he heard of medications to help with his symptoms but does not want to have to plan out his intimate moments.

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D. Bupropion

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Questions

120

2012 Updates in Therapeutics:

The Pharmacotherapy Preparatory Review & Recertification Course

Pharmacokinetics: A Refresher

Curtis L. Smith, Pharm.D., BCPS
Ferris State University

Conflict of Interest Disclosures

Curtis Smith, Pharm.D.

- **I have no conflicts of interest related to this presentation.**

Learning Objectives

- Identify and provide examples using basic pharmacokinetic concepts commonly used in clinical practice, including elimination rate constant, volume of distribution (Vd), clearance, and bioavailability.

Page Number (Page number for the answer to Patient Case if applicable)

Learning Objectives

- Describe specific pharmacokinetic characteristics of commonly used therapeutic agents, including aminoglycosides, vancomycin, phenytoin, and digoxin, as well as pharmacokinetic alterations in patients with renal and hepatic disease.
- Define important issues as they pertain to drug concentration sampling and interpretation.

Page Number (Page number for the answer to Patient Case if applicable)

Agenda

- Basic Pharmacokinetic Relationships
- ADME
- Non-Linear Pharmacokinetics
- Noncompartmental Pharmacokinetics
- Data Collection and Analysis
- Pharmacokinetics in Renal/Hepatic Disease
- Pharmacodynamics

Table of PK terms on Page 117 of the handout

Page Number (Page number for the answer to Patient Case if applicable)

Basic PK Relationships

- HR is receiving vancomycin for MRSA
- HR has renal failure
- Dosing:
  - 1g on 3/21 at 1200
  - Concentration on 3/21 at 1400 = 23.8 mg/L
  - Concentration on 3/24 at 1400 = 12.1 mg/L

94 (119)

Basic PK Relationships

If you were to give a 1g dose on 3/24 at 1600 when would you need to give the next dose?

A. One day after the dose on the 24th

B. Three days from the dose on the 24th

C. Six days from the dose on the 24th

D. There is insufficient information to calculate when to redose

94 (119)

Basic PK Relationships

- rapid IV (or oral) bolus: $Vd = \frac{F * dose}{Cp_0}$
- Vd = 1000mg / 23.8mg/L = 42L

94 (119)

Basic PK Relationships

- elimination rate constant – $k = \frac{(\ln C_1 - \ln C_2)}{(t_1 - t_2)}$
- or $t_{1/2} = \frac{0.693}{k}$
- k = (ln 23.8mg/L – ln 12.1mg/L) / 72 hours = 0.0094/hr

95 (119)

Basic PK Relationships

- ΔConc. = 1000mg / 42L = 23.8mg/L
- 12.1mg/L + 23.8mg/L ~ 36mg/L
- 10mg/L = 36mg/L * $e^{-0.0094*t}$
  t = 136 hours or ~ 6 days
- or in 1 half life the concentration ↓ to 18mg/L and in another to 9 mg/L – since half life is 3 days, wait 6 days

95 (119)

Basic PK Relationships

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94 (119)

Basic PK Relationships

Following administration of 100mg of a drug IV and 200mg of the same drug PO, the AUCs are 50mg/L/hr and 25mg/L/hr. What is the bioavailability of this drug?

A. 25%

B. 37.5%

C. 50%

D. 100%

94 (119)

Basic PK Relationships

- $F = \frac{Dose_{iv} * AUC_{ev}}{Dose_{ev} * AUC_{iv}}$
- F = (100mg * 25mg/L/hr) / (200mg * 50mg/L/hr)
- F = 25% (A)

94 (119)

Basic PK Relationships

- LB is receiving tobramycin for *Pseudomonas* pneumonia
- LB has renal failure
- Dosing:
  - 160mg at 1200
  - Concentration at 1800 = 6.5 mg/L
  - Concentration next day at 0600 = 5.4 mg/L

94 (119)

Basic PK Relationships

When L.B.'s concentration is 1 mg/L, what dose is needed to achieve a peak of 9 mg/L?

A. 140mg
B. 160mg
C. 180mg
D. 200mg

94 (119)

Basic PK Relationships

- elimination rate constant – $k = \frac{(\ln C_1 - \ln C_2)}{(t_1 - t_2)}$
- or $t_{1/2} = \frac{0.693}{k}$
- k = (ln 6.5mg/L – ln 5.4mg/L) / 12 hours = 0.015/hr
- Concentration at end of the infusion:
  - $Cp_0 = C_1 / e^{-kt}$
  - $Cp_0 = 6.5 / e^{-(0.015*5)}$ Cp_0 = 7 mg/L

95 (119)

Basic PK Relationships

- rapid IV (or oral) bolus: $Vd = \frac{F * dose}{Cp_0}$
- Vd = 160mg / 7mg/L = 22.9L
- rapid IV (or oral) bolus: Dose = Δ Cp * Vd
- Dose = 8 mg/L / 22.9L = 183.2 mg

95 (119)

Basic PK Relationships

When L.B.'s concentration is 1 mg/L, what dose is needed to achieve a peak of 9 mg/L?

A. 140mg
B. 160mg
C. 180mg
D. 200mg

94 (119)

Absorption

- First Pass Effect
  - Blood perfusing GI tissues passes through liver
  - Buccal and some rectal blood bypasses liver
- Enterohepatic Recirculation
  - Drugs excreted in bile, metabolized by normal flora and reabsorbed back into circulation
  - Drug expelled by gall bladder on sight, smell or ingestion of food

95-96

Absorption

P-glycoprotein:

A. is a plasma protein that binds basic drugs.

B. transfers drugs through the GI mucosa, increasing absorption.

C. diminishes the effect of CYP3A4 in the GI mucosa.

D. is an efflux pump that decreases GI mucosa absorption.

96 (119)

Absorption

- P-glycoprotein:
  - CYP3A4 and P-glycoprotein in GI mucosa work together to decrease absorption
  - efflux pump that pumps drug back into the GI lumen – absorption drug interactions
  - most CYP3A4 substrates are also P-glycoprotein substrates
  - many CYP3A4 inhibitors/inducers also inhibit/induce P-glycoprotein
  - example: verapamil or amiodarone or dronedarone and digoxin or dabigatran

96

Absorption

P-glycoprotein:

A. is a plasma protein that binds basic drugs.

B. transfers drugs through the GI mucosa, increasing absorption.

C. diminishes the effect of CYP3A4 in the GI mucosa.

D. is an efflux pump that decreases GI mucosa absorption.

96 (119)

Distribution

- Volume of Distribution
  - Constant that relates the amount of drug in the body to an observed concentration of drug
  - $Vd = \frac{F * dose}{Cp_0}$

97

Distribution

- Protein Binding
  - Albumin
  - Alpha-1-acid glycoprotein
  - Lipoprotein
- P-glycoprotein

97

Clearance

- Enzymes Involved in Drug Metabolism
  - Oxygenases, Hydrolytic and Conjugating Enzymes
  - Table 3
- Drug Transport Proteins
  - SLC and ABC Superfamilies
  - Table 4

97-98

Clearance

Renal transplant with CAP, also receiving cyclosporine. Which of the following would be the least likely to interact?

A. Erythromycin

B. Clarithromycin

C. Azithromycin

D. all macrolides inhibit CYP3A4

99 (119)

Clearance

- Cytochrome P450
  - a group of heme-containing enzymes responsible for phase 1 metabolic reactions
  - located in endoplasmic reticulum in 1) liver, 2) small intestine, and 3) brain, lung, kidney
  - drugs generally have a high affinity for one CYP450 but may utilize secondary pathways

* See table on page 116

98

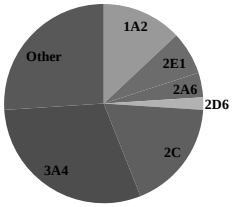
Clearance

CYP 3 A 4

99

Clearance

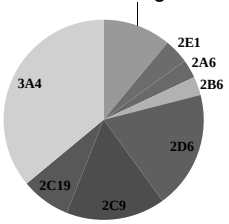
- Cytochrome P450
  - Content of CYP450 enzymes in the liver



100

Clearance

- Cytochrome P450
  - Role in CYP-mediated drug elimination



100

Clearance

- Cytochrome P450 characteristics
  - inhibition is substrate independent
  - some substrates are metabolized by more than one CYP450
  - enantiomers may be metabolized by different CYP450
  - differences in inhibition may exist in the same drug class

100

Clearance

- Cytochrome P450 characteristics
  - substrates can also be inhibitors
  - most inducers and some inhibitors can affect more than one isozyme
  - inhibitors may affect different isozymes at different doses

100

Clearance

Renal transplant with CAP, also receiving cyclosporine. Which of the following would be the least likely to interact?

A. Erythromycin

B. Clarithromycin

C. Azithromycin

D. all macrolides inhibit CYP3A4

99 (119)

Clearance

Renal transplant with CAP, also receiving cyclosporine. Which of the following would be the least likely to interact?

A. Erythromycin

B. Clarithromycin

C. Azithromycin

D. all macrolides inhibit CYP3A4

99 (119)

Pharmacogenetics

- Definition: more than one genetic variant (alleles) which are stable components in the population (>1% of population)
- generally poor and extensive metabolizers
- antimode: separation between 2 populations
- phenotype – clinical expression of the trait
- genotype – genetic composition
- CYP2D6, CYP2C19, n-acetyltransferase, CYP2C9

101-102

Non-linear Pharmacokinetics

- CM is a 55 year old male
- Started on phenytoin, 200mg daily, post craniotomy.
- Recent steady state concentration = 6 mg/L

102 (119)

Nonlinear Pharmacokinetics

If CMs Km is calculated to be 5 mg/L, what will most likely occur if the dose is doubled (to 400mg po daily)?

A. His concentration will double since phenytoin clearance is linear above the Km.
B. His concentration will more than double since phenytoin clearance is non-linear above the Km.
C. His concentration will not change because phenytoin is an auto inducer and clearance increases with time.
D. His concentration will increase by only 50% since phenytoin absorption decreases significantly with doses greater than 300mg.

102 (119)

Non-linear Pharmacokinetics

- Non-linear elimination
  - saturation or partial saturation of the elimination pathway
  - Michaelis-Menten equation:
  - rate of elimination = $\frac{Vmax * C}{Km + C}$
  - non-linearity occurs when concentration is at or above K_m

102-103

Nonlinear Pharmacokinetics

If CMs Km is calculated to be 5 mg/L, what will most likely occur if the dose is doubled (to 400mg po daily)?

A. His concentration will double since phenytoin clearance is linear above the Km.
B. His concentration will more than double since phenytoin clearance is non-linear above the Km.
C. His concentration will not change because phenytoin is an auto inducer and clearance increases with time.
D. His concentration will increase by only 50% since phenytoin absorption decreases significantly with doses greater than 300mg.

102 (119)

Noncompartmental PK

- Why?
  - ID of the "correct" model is difficult
  - Compartmental view is unrealistic
  - Linear regression is unnecessary
  - Requires fewer and less stringent assumptions
  - More general methods and equations
  - Matching data to compartments unnecessary

103

Noncompartmental PK

$$AUC = \sum \frac{(Cn+1 + Cn)}{2} * (t_{n+1} - t_n) \ldots + \frac{Clast}{k}$$

$$AUMC = \sum \frac{(Cn+1 * tn+1 + Cn * tn)}{2} * (t_{n+1} - t_n) \ldots + \frac{Clast * tlast}{k} + \frac{Clast}{k^2}$$

$$MRT = \frac{AUMC}{AUC}$$

103

Noncompartmental PK

$$Cl = \frac{Dose}{AUC}$$

$$Vss = \frac{Dose * AUMC}{AUC^2}$$

$$k = \frac{1}{MRT}$$

$$k_a = \frac{1}{MAT}$$

104

Data Collection and Analysis

- RK 54 y/o F with DM and ESRD
- Receiving gentamicin for pneumonia

Which is true re: post dialysis sample?

A. Obtain conc. immediately following HD.
B. Wait a few hours to obtain the conc. since the conc. will ↓ significantly within the first few hours after HD.
C. Wait a few hours to obtain the conc. since the conc. will ↑ significantly within the first few hours after HD.
D. Wait until the next day so that all of the effects of hemodialysis have abated.

104 (119)

Data Collection and Analysis

- Timing of collection
  - ensure completion of absorption / distribution
  - ensure completion of redistribution post HD (especially with high flux/high efficiency)
- Specimen requirements
  - whole blood
  - plasma
  - serum

104

Data Collection and Analysis

- RK 54 y/o F with DM and ESRD
- Receiving gentamicin for pneumonia

Which is true re: post dialysis sample?

A. Obtain conc. immediately following HD.
B. Wait a few hours to obtain the conc. since the conc. will ↓ significantly within the first few hours after HD.
C. Wait a few hours to obtain the conc. since the conc. will ↑ significantly within the first few hours after HD.
D. Wait until the next day so that all of the effects of hemodialysis have abated.

104 (119)

Data Collection and Analysis

A drug assay is touted as having high specificity but low sensitivity. This means:

A. The assay can't distinguish the drug from like products, but can detect extremely low concs.
B. The assay can't distinguish the drug from like products, and can't detect extremely low concs.
C. The assay can distinguish the drug from like products, and can detect extremely low concs.
D. The assay can distinguish the drug from like products, but can't detect extremely low concs.

105 (119)

Data Collection and Analysis

- Assay Terminology
  - Precision (reproducibility)
    - SD and CV
  - Accuracy
    - Correlation coefficient
  - Predictive performance (accuracy)
    - Precision and bias
  - Sensitivity
  - Specificity

105

Data Collection and Analysis

A drug assay is touted as having high specificity but low sensitivity. This means:

A. The assay can't distinguish the drug from like products, but can detect extremely low concs.
B. The assay can't distinguish the drug from like products, and can't detect extremely low concs.
C. The assay can distinguish the drug from like products, and can detect extremely low concs.
D. The assay can distinguish the drug from like products, but can't detect extremely low concs.

105 (119)

Data Collection and Analysis

- Assay Methodology
  - Immunoassays
    - Radioimmunoassay
      - Advantages: extremely sensitive
      - Disadvantages: short half-life, nuclear waste, cross reactivity
    - Enzyme immunoassay (EMIT)
    - Fluorescence immunoassay (FPIA)
      - Advantages: simple, automated, highly sensitive, stable
      - Disadvantages: background interference

106

Data Collection and Analysis

- Assay Methodology
  - HPLC
  - Gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry
  - Flame photometry
  - Bioassay

106

Population Pharmacokinetics

- Population pharmacokinetics useful:
  - complicated dosing regimens
  - drug concentrations obtained before steady state
  - only a few drug concentrations are feasibly obtained
- Bayesian pharmacokinetics
  - prior population information is combined with patient specific data for predicting
  - with small amounts of individual data Bayesian forecasting generally yields more precise results

106

PK in Renal Disease

- KM is an 80 year old female (52kg, 5'4")
- Admitted for pyelonephritis with sepsis
- PMH: MI x2, CHF, HTN, osteoporosis, rheumatoid arthritis, CVA
- Serum creatinine: 0.92 mg/dl; albumin 2.9 g/dl
- Drugs: TMP/SMZ 280mg IV q12h, lisinopril 10mg po daily, digoxin 0.125mg po daily, furosemide 40mg po daily, cimetidine 400mg po BID, APAP 650mg po q6h, $CaCO_3$, and carvedilol 6.25mg po BID

106 (119)

PK in Renal Disease

KMs approximate glomerular filtration rate is:

A. 10 ml/min/1.73m^2

B. 30 ml/min/1.73m^2

C. 60 ml/min/1.73m^2

D. 120 ml/min/1.73m^2

106 (119)

PK in Renal Disease

KMs approximate glomerular filtration rate is:

A. 10 ml/min/1.73m^2

B. 30 ml/min/1.73m^2

C. 60 ml/min/1.73m^2

D. 120 ml/min/1.73m^2

106 (119)

PK in Renal Disease

Which of KMs drugs may alter serum creatinine concentrations?

A. Lisinopril and digoxin

B. Trimethoprim/sulfamethoxazole and cimetidine

C. Furosemide and calcium carbonate

D. Acetaminophen and carvedilol

106 (119)

PK in Renal Disease

- Estimation of GFR / Creatinine Clearance
  - Creatinine production and elimination
  - Calculated CrCl by 24 hour urine
  - Creatinine clearance estimation
    - Jelliffe
    - Cockcroft and Gault
    - Schwartz and Shull (pediatric)
  - GFR estimation
    - MDRD study equation (standardized creatinine)
    - Chronic Kidney Disease Epidemiology Collaboration equation (CKD-Epi)

107-109

PK in Renal Disease

- Factors influencing estimates of creatinine clearance
  - Disease states / clinical conditions
  - Diet
  - Drugs / endogenous substances
    - Laboratory interaction
    - Pharmacokinetic interaction

109

PK in Renal Disease

- Drug dosing in renal disease
  - Loading doses
  - Maintenance doses
    - Changing the dosing interval
    - Changing the dose

110

PK in Renal Disease

KMs estimated CrCl is:

Use IBW when BMI > 30 kg/m^2

$$\text{CrCl (ml/min)} = \frac{(140 - \text{Age}) * \text{TBW}}{\text{Scr} * 72} * 0.85$$

KMs estimated GFR is:

MDRD (ml/min/1.73m^2) = 175 * (SCr)$^{-1.154}$ * (age in years)$^{-0.203}$ * 1.212 (if patient is African American) * 0.742 (if patient is a woman)

106 (119)

PK in Renal Disease

KMs approximate glomerular filtration rate is:

A. 10 ml/min/1.73m^2

B. 30 ml/min/1.73m^2

C. 60 ml/min/1.73m^2

D. 120 ml/min/1.73m^2

106 (119)

PK in Renal Disease

Which of KMs drugs may alter serum creatinine concentrations?

A. Lisinopril and digoxin

B. Trimethoprim/sulfamethoxazole and cimetidine

C. Furosemide and calcium carbonate

D. Acetaminophen and carvedilol

106 (119)

PK in Hepatic Disease

- SJ is a 55 year old male with fungemia
- PMH: hepatic dysfunction – ascites, no encephalopathy
- Started on caspofungin – decrease dose in patients with Child-Pugh score of 7 to 9
- Labs: AST = 85U/L, ALT = 56U/L, Alk phos = 190U/L, total bilirubin = 1.8mg/dl, albumin = 2.9g/dl, LDH = 270U/L, PT/INR = 14.6/1.7, GGT = 60U/L

110 (119)

PK in Hepatic Disease

What is his Child-Pugh score?

A. 3

B. 5

C. 8

D. 11

110 (119)

PK in Hepatic Disease

- Rules for dosing in hepatic disease
  - High ER drugs affected more than low ER drugs
  - Conjugation maintained in liver disease
  - Start low and increase dose slowly

110-111

PK in Hepatic Disease

- Child-Pugh Classification for Liver Disease

	Points		
	1	2	3
Encephalopathy	0	1 or 2	3 or 4
Ascites	0	+	++
Bilirubin (mg/dL)	< 1.5	1.5-2.3	> 2.3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (seconds over control)	0-4	4-6	> 6

111

PK in Hepatic Disease

What is his Child-Pugh score?

A. 3

B. 5

C. 8

D. 11

110 (119)

Pharmacodynamics

Which of the following is a reason for a drug to follow clockwise hysteresis?

A. Formation of an active metabolite

B. Delay in equilibrium between the blood and the site of action

C. Tolerance

D. Increased sensitivity with time

111 (120)

Pharmacodynamics

- Definition – relationship between concentration and response
- Hill equation

$$E = \frac{(E_{max}) * (C^{\gamma})}{EC_{50}^{\gamma} + C^{\gamma}}$$

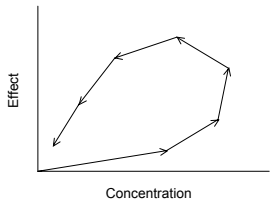
E = pharmacologic response
Emax = maximum drug effect
EC_{50} = concentration producing half of the max effect
γ = factor that accommodates the shape of the curve

- Hysteresis Loops
  - Definition: concentrations late after a dose produce an effect different from that produced by the same concentration soon after the dose

111-112

Pharmacodynamics

- Counterclockwise Hysteresis

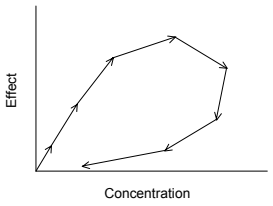


Causes:
1. Increased sensitivity
2. Formation of an active metabolite
3. Delay in equilibrium between plasma concentrations and the concentration at the site of action
4. Example: digoxin

112

Pharmacodynamics

- Clockwise Hysteresis



Causes:
1. Tolerance
2. Formation of an inhibitory metabolite
3. Equilibrium reached faster between arterial blood and site of action vs. venous blood and site of action
4. Example: Pseudoephedrine, cocaine

113

Drug PK Information

Which of the following is a reason for a drug to follow clockwise hysteresis?

A. Formation of an active metabolite

B. Delay in equilibrium between the blood and the site of action

C. Tolerance

D. Increased sensitivity with time

111 (120)

Drug PK Information

- PL is a 45 y/o male with CRF
- Phenytoin 400mg/day for seizures
- Labs:
  - Phenytoin concentration = 13.6 mg/L
  - Albumin concentration = 4.2 g/dL

114 (120)

Drug PK Information

What do you recommend to do with his dose?

A. Make no changes in his current drug regimen.

B. Keep the total daily dose the same but change the regimen to 200mg BID.

C. Increase the dose for better seizure control.

D. Decrease the dose to prevent toxicity.

114 (120)

Drug PK Information

DRUG	THERA-PEUTIC RANGE	SAMPLING ISSUES	COMMENTS
Phenytoin	10-20 mg/L Free: 1-2 mg/L	Generally obtain trough concentrations	% free increases with renal failure and hypoalbuminemia; induces liver enzymes; susceptible to metabolic drug interactions
Carbamazepine	4-12 mg/L		Autoinduction; active metabolite 10,11 epoxide
Phenobarbital	15-40 mg/L		Enzyme inducer
Valproic acid	50-100 mg/L		Saturable protein binding; % free increases with renal failure and hypoalbuminemia

115

Drug PK Information

- Equations to correct for increased free fraction of phenytoin:
  - For changes in albumin:

$$Cp = \frac{Cp'}{(0.9 * \frac{Alb}{4.4}) + 0.1}$$

  - For changes in albumin and/or renal function:

$$Cp = \frac{Cp'}{(0.48 * 0.9 * \frac{Alb}{4.4}) + 0.1}$$

115

Drug PK Information

What do you recommend to do with his dose?

A. Make no changes in his current drug regimen.

B. Keep the total daily dose the same but change the regimen to 200mg BID.

C. Increase the dose for better seizure control.

D. Decrease the dose to prevent toxicity.

114 (120)

Drug PK Information

- NR - 63 y/o male, renal insufficiency
- A fib, HR=120, digoxin - rate control

Which of the following is correct?

A. LD same, MD decreased.

B. LD decreased, MD same.

C. Neither dose should be changed.

D. Both doses should be changed.

114 (120)

Drug PK Information

DRUG	THERA-PEUTIC RANGE	SAMPLING ISSUES	COMMENTS
Digoxin	0.8-2.0 mcg/L	Prolonged distribution period necessitates sampling > 6-12 hours post dose	Vd decreases in renal disease; susceptible to drug interactions
Lidocaine	2-6 mg/L		Difficult to interpret due to binding to AAG and Vd changes in CHF and AMI
Procainamide	4-12 mg/L		Active metabolite NAPA with poorly defined therapeutic range
Quinidine	2-5 mg/L		

115

Drug PK Information

- NR - 63 y/o male, renal insufficiency
- A fib, HR=120, digoxin - rate control

Which of the following is correct?

A. LD same, MD decreased.

B. LD decreased, MD same.

C. Neither dose should be changed.

D. Both doses should be changed.

114 (120)

Drug PK Information

- PP - 34 year old male with CP and UTIs
- Tobramycin 400mg IV daily

This high dose, extended interval regimen:

A. takes advantage of the aminoglycoside's concentration dependent killing.

B. is more efficacious than standard dosing.

C. does not require concentration monitoring.

D. will not cause nephrotoxicity.

114 (120)

Drug PK Information

DRUG	THERAPEUTIC RANGE	SAMPLING ISSUES	COMMENTS
Amino-glycosides	Cp_{max} = 4-10 mg/L (Amikacin = 20-30 mg/L) Cp_{min} < 2 mg/L (Amikacin = 10 mg/L)	Duration of infusion, timing of first sample post-infusion (generally should be 0.5-1 hour)	Be familiar with Sawchuk-Zaske method and high-dose, extended-interval dosing
Vancomycin	Cp_{min} = 10-20 mg/L	Controversial whether to obtain peaks or concentrations altogether	Vancomycin TDM guidelines – CID 2009

115

Drug PK Information

- PP - 34 year old male with CP and UTIs
- Tobramycin 400mg IV daily

This high dose, extended interval regimen:

A. takes advantage of the aminoglycoside's concentration dependent killing.

B. is more efficacious than standard dosing.

C. does not require concentration monitoring.

D. will not cause nephrotoxicity.

114 (120)

Drug PK Information

DRUG	THERAPEUTIC RANGE	SAMPLING ISSUES	COMMENTS
Cyclosporine	100-250 mcg/L	Whole blood samples	Many drug interactions
Lithium	0.3-1.3 mmol/L	Prolonged distribution necessitates sampling 12 hours post dose	
Theophylline	10-20 mg/L		Treat as continuous infusion with sustained release dosage forms

115

Questions / Comments

Suggested References - Page 118
Self-assessment Questions - Pages 92-93
Answers to Self-assessment Questions - Page 121

Self Assessment Questions

1. Which of the following statements is true regarding the tobramycin?

   a. There are sufficient data to determine the t1/2, but not the Vd
   b. There are sufficient data to determine both the t1/2 and Vd.
   c. There are insufficient data to determine either the t1/2 or the Vd.
   d. There are sufficient data to determine the Vd, but not the t1/2.

Self Assessment Questions

1. Which of the following statements is true regarding the tobramycin?

   a. There are sufficient data to determine the t1/2, but not the Vd
   b. There are sufficient data to determine both the t1/2 and Vd.
   c. There are insufficient data to determine either the t1/2 or the Vd.
   d. There are sufficient data to determine the Vd, but not the t1/2.

Self Assessment Questions

2. Which of the following best describes this patient's gentamicin pharmacokinetic parameters?

   a. The $t_{1/2}$ is about 2 hours.
   b. The $t_{1/2}$ is about 3 hours.
   c. The maximum concentration is about 3.8 mg/L.
   d. The volume of distribution is about 11.6L.

Self Assessment Questions

2. Which of the following best describes this patient's gentamicin pharmacokinetic parameters?

   a. The $t_{1/2}$ is about 2 hours.
   b. The $t_{1/2}$ is about 3 hours.
   c. The maximum concentration is about 3.8 mg/L.
   d. The volume of distribution is about 11.6L.

Self Assessment Questions

3. What probably happened to the gentamicin half-life in RO during her hospitalization?
   a. Her clearance increased which increased her volume of distribution and decreased her half-life.
   b. Her Cl increased which increased her ke and decreased her half-life.
   c. Her Vd decreased which increased her clearance and decreased her half-life.
   d. Her Vd decreased which increased her ke and increased her half-life.

Self Assessment Questions

3. What probably happened to the gentamicin half-life in RO during her hospitalization?
   a. Her clearance increased which increased her volume of distribution and decreased her half-life.
   b. Her Cl increased which increased her ke and decreased her half-life.
   c. Her Vd decreased which increased her clearance and decreased her half-life.
   d. Her Vd decreased which increased her ke and increased her half-life.

Self Assessment Questions

4. Which of the following regimens would be best for this patient if goal trough is 10-15 mg/L?

a. Maintain the dose at 1000mg IV every 24 hours.
b. Lower the dose to 500mg but keep the interval at every 24 hours.
c. Keep the dose at 1000mg but shorten the interval to every 12 hours.
d. Lower the dose to 500mg and shorten the interval to every 12 hours.

Self Assessment Questions

4. Which of the following regimens would be best for this patient if goal trough is 10-15 mg/L?

a. Maintain the dose at 1000mg IV every 24 hours.
b. Lower the dose to 500mg but keep the interval at every 24 hours.
c. Keep the dose at 1000mg but shorten the interval to every 12 hours.
d. Lower the dose to 500mg and shorten the interval to every 12 hours.

Self Assessment Questions

5. What would be the most appropriate regimen for this patient?

a. Theophylline SR 300mg po every 12 hours.
b. Theophylline SR 600mg po every 12 hours.
c. Theophylline SR 400mg po every 8 hours.
d. Theophylline SR 600mg po every 8 hours.

Self Assessment Questions

5. What would be the most appropriate regimen for this patient?

a. Theophylline SR 300mg po every 12 hours.
b. Theophylline SR 600mg po every 12 hours.
c. Theophylline SR 400mg po every 8 hours.
d. Theophylline SR 600mg po every 8 hours.

Self Assessment Questions

6. What is your recommendation?

a. Increase the dose to 200mg IV TID.
b. Increase the dose to 200mg IV BID.
c. Decrease the dose to 100mg IV BID.
d. Keep the dose the same.

Self Assessment Questions

6. What is your recommendation?

a. Increase the dose to 200mg IV TID.
b. Increase the dose to 200mg IV BID.
c. Decrease the dose to 100mg IV BID.
d. Keep the dose the same.

Self Assessment Questions

7. You are asked about the TDx and EMIT assays. Which one of the statements is most correct?

   a. Both are immunoassays; one labels antibody while the other labels antigen.
   b. Both are immunoassays; one uses antibody as a marker and the other a radioisotope.
   c. Both are immunoassays; one uses an enzyme label while the other uses a fluorescent label.
   d. They are both names for the same assay technique.

Self Assessment Questions

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Self Assessment Questions

8. Which of the following statements best describes what should be done next?

   a. Admit the patient for administration of digoxin Fab.
   b. Tell the patient to skip tomorrow's dose of digoxin and begin 0.125 mg po daily.
   c. Administer a dose of activated charcoal.
   d. Do nothing today regarding the digoxin.

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9. A research group is analyzing the relationship between various independent patient demographics and phenytoin pharmacokinetics. Which of the following statistical tests will need to be employed?

   a. One-way ANOVA
   b. Analysis of Covariance (ANCOVA)
   c. Multiple logistic regression
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Self Assessment Questions

10. NT is receiving valproic acid. Trough = 22 mg/L. Albumin = 4.1 g/dl. What recommendation would you make concerning her dose?
    a. Continue with current dose, the concentration is close enough to the therapeutic range.
    b. Assess compliance and increase her dose, the concentration is below the therapeutic range.
    c. Decrease her dose, the concentration is slightly above the therapeutic range.
    d. Assess compliance then check a free valproic acid concentration and adjust accordingly.

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