Principles of Medication Use in Older Adults

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Disclosures

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Learning Objectives

- Evaluate the potential effects of physiologic changes on the pharmacokinetics and pharmacodynamics of common medications in healthy & frail older adults; and

- Apply knowledge of altered pharmacokinetics and pharmacodynamics to the care of older adults.
My Guiding Principles

- Older adults are a heterogeneous group.
- Disease burden is more important than chronologic age.
- “Elderly” in phase 3 studies of investigational drugs are essentially “middle-aged” adults.
- Older adults suffer when a “usual” dosage of a “new” drug is used.
- Adverse drug reactions in older adults may present in unexpected ways such as impaired continence, cognition, and mobility.
Aging and PK and PD Changes

- Age-related changes versus concomitant disease and drug-related changes

- Physiologic changes and pharmacokinetics
  - Absorption
  - Distribution
  - Metabolism
  - Renal elimination

- Physiologic changes and pharmacodynamics
## Aging and Drug Absorption

<table>
<thead>
<tr>
<th>System</th>
<th>Potential Physiologic Changes</th>
<th>Potential Effect on Absorption</th>
</tr>
</thead>
</table>
| Gastrointestinal | ↗ stomach pH (less acidic)  
                  ↓ gastrointestinal blood flow  
                  Slowed gastric emptying  
                  Slowed gastrointestinal transit | ↓ absorption of some drugs and nutrients  
                  ↓ first-pass extraction/metabolism  
                  Rate of absorption may be ↓ |
| Skin           | Thinning of dermis  
                  Loss of subcutaneous fat | ↓ or no change to drug reservoir formation with transdermal products |
Changes in Drug Absorption

- What does the available evidence suggest?
- Iron, calcium, and B12 might be ↓
- Passive diffusion is ⇔
- Caution w/ transdermal formulations in people who are ~ 50 kg or less
- Consider effects of concomitant diseases and drugs
  - HF
  - CKD
“First Pass” Extraction

- Effects on presystemic clearance
  - Some ("high extraction" drugs) are removed by the liver before entering systemic circulation
    - Example: Morphine
- Potential changes in older adults
  - Due to decreased hepatic blood flow and liver mass, more drug may enter systemic circulation
    - Examples: Labetalol, verapamil, morphine
  - If a drug is a “pro-drug”, less may be in the active form in systemic circulation
## Aging and Drug Distribution

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Physiologic Change with Aging</th>
<th>Effect on Pharmacokinetics</th>
</tr>
</thead>
</table>
| Body composition     | ↓ total body water  
                        ↓ lean body mass  
                        ↑ body fat  
                        ↓ or unchanged serum albumin  
                        ↑ α1-acid glycoprotein  
                        ↑ Increased BBB permeability?                                 | ↑ Vd and accumulation of lipid-soluble drugs  
                                        ↑ fraction of free fraction of highly bound acidic drugs  
                                        ↓ free fraction of basic drugs                   |
Aging and Drug Distribution

- Age-related physiologic changes
  - Increased proportion of adipose tissue
    - Young men: 18% of body mass is adipose tissue & increases to 36% in elderly men
    - Young women: 36% of body mass is adipose tissue & increases to 48% in elderly women
Aging and Drug Distribution

• Serum albumin
  • Highly protein bound drugs may have ↑ proportion of free drug
  • “Free” / unbound drug is available for drug action
  • Drug assays report total drug unless specific for free levels

• Influence of concomitant diseases
  • Chronic renal failure and phenytoin
    • 79 year old man w/ seizure disorder treated with phenytoin 300mg per day. Phenytoin level 5.7 mg/dl, but without seizures. PMH significant for CKD, albumin level of 2.8gm/dl. Should the dose be doubled?
Aging and Drug Metabolism

- Sites of drug metabolism include GI tract and kidney, as well as the liver
- Assessing hepatic function: How can we do this and what are the limitations?
- Age-related physiologic changes
  - Decreased hepatic blood flow
  - Decreased liver mass
  - Effects on hepatic microsomal activity
  - Oxidative phase I reactions(?)
# CYP Families & Drug Interactions

<table>
<thead>
<tr>
<th>Substrate</th>
<th>CYP 1A2</th>
<th>CYP 2C9</th>
<th>CYP 2D6</th>
<th>CYP 3A4</th>
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</thead>
<tbody>
<tr>
<td>R-warfarin</td>
<td>Ciprofloxacin</td>
<td>Amiodarone</td>
<td>Amiodarone</td>
<td>Rifampin</td>
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<tr>
<td>Phenytoin</td>
<td>Cimetidine</td>
<td>Fluconazole</td>
<td>Fluconazole</td>
<td>Aprepitant</td>
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<tr>
<td>Glipizide</td>
<td>Celecoxib</td>
<td>Paroxetine</td>
<td>Ritonavir</td>
<td>Rifampin</td>
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<tr>
<td>Theophylline</td>
<td>Theophylline</td>
<td>Celecoxib</td>
<td>Oxycodone</td>
<td>Rifampin</td>
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<tr>
<td>S-warfarin</td>
<td>Losartan</td>
<td>Metoclopramide</td>
<td>Erythromycin</td>
<td>Rifampin</td>
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<tr>
<td>Clozapine</td>
<td>Fluoxetine</td>
<td>Metoprolol</td>
<td>Diltiazem</td>
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Aging and Renal Drug Elimination

- NIA Baltimore Longitudinal Study on Aging
  - Successful vs. usual aging
- Age-related physiologic changes in renal function
  - ↓ GFR, renal plasma flow, renal tubular secretion
- Related considerations
  - Thirst perception, ↑ ADH secretion, ↓ ability to concentrate urine
Creatinine-Based Equations

- Creatinine is influenced by factors other than GFR

- Accuracy is an issue with both eGFR and eCrCl in individuals with extremes of body size or muscle mass

- Creatinine-based estimate requires that kidney function be stable.

- Should we substitute “1” for the actual SCr in frail elderly?
## Estimation of Renal Elimination for 5’5”, 55 kg Woman

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<th>Age (years)</th>
<th>SCr (mg/dl)</th>
<th>eCrCl (ml/min)</th>
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<tr>
<td>30</td>
<td>1.1</td>
<td>65</td>
</tr>
<tr>
<td>50</td>
<td>1.1</td>
<td>53</td>
</tr>
<tr>
<td>70</td>
<td>1.1</td>
<td>41</td>
</tr>
<tr>
<td>90</td>
<td>1.1</td>
<td>30</td>
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Creatinine Clearance

- Cockcroft-Gault equation
  - Actual or ideal body weight?
  - Inaccurate for elderly bedridden patients
  - Inaccurate for individuals with muscle wasting conditions
- MDRD equation
  - Should we use this instead of CG?
Aging-Related Changes and Pharmacodynamics
Aging and Pharmacodynamics

- Variable effects on overall homeostasis
- Cardiovascular system
  - ↓ responsiveness of cardiac beta receptors to beta-blockers
  - ↑ sensitivity to drugs that prolong QT interval
  - ↑ risk of orthostatic hypotension from antihypertensive agents
  - Changes in sodium and water regulation
Aging and Pharmacodynamics

- **Respiratory system**
  - ↓ responsiveness to inhaled beta-agonists?

- **Central nervous system**
  - ↑ sensitivity to anticholinergic drugs
  - ↑ blood-brain barrier permeability
  - ↑ CNS reaction time
  - ↑ psychomotor retardation
Drug-receptor interaction
Brain receptors become more sensitive, making psychoactive drugs very potent.

Circulation
Vascular nerve control is less stable. Antihypertensives, for example, may overshoot, dropping blood pressure too low. Digoxin, for example, may slow the heart rate too much.

Metabolism
Liver mass shrinks. Hepatic blood flow and enzyme activity decline. Metabolism drops to 1/2 to 2/3 the rate of young adults. Enzymes lose ability to process some drugs, thus prolonging drug half-life.

Excretion
In kidneys, renal blood flow, glomerular filtration rate, renal tubular secretion and reabsorption, and number of functional nephrons decline. Blood flow and waste removal slow. Age-related changes lengthen half-life for renally excreted drugs. Oral antidiabetic drugs, among others, stay in the body longer.

Absorption
Gastric emptying rate and gastrointestinal motility slow. Absorption capacity of cells and active transport mechanism decline.

Distribution
Lean body mass falls. Adipose stores increase. Total body water declines, raising the concentration of water-soluble drugs, such as digoxin, which can cause heart dysfunction. Plasma protein diminishes, reducing sites available for protein-bound drugs and raises blood levels of free drug.
Patient Examples
Aging and PK/PD Changes: Now Add The “Usual Dose” in a Busy Office Practice

- A 79 year old woman was admitted to a local hospital with altered mental status and visual hallucinations. HPI was significant for the use of valciclovir 1gm TID prior to admission for new onset of herpes zoster infection. A UTI was also diagnosed and ciprofloxacin was added to her drug regimen. PMH included CKD, DM, BAKA, CAD, and hyperlipidemia.

- A 94 year old man was admitted to a local hospital unresponsive. PMH was significant only for well controlled T2DM and several other chronic conditions. He was recently started on gabapentin 600mg TID for neuropathic pain.

- Where do “geriatric” dosing recommendations come from?
86 year old woman admitted for pneumonia. PMH was significant for seizure disorder, but taking no meds. Pt started on cefuroxime 1.5 gm IV q8h. She experienced a generalized seizure 4 days after admission.

She received a 1000 mg IV phenytoin load, then 300 mg QD was started. 2 days later the serum phenytoin conc. was 27 mcg/ml.

Why might this have happened? What other information do you need?
An Example of Real Clinical Complexity (NEJM 2004; 351:2827)

- A 62-year-old man with a history of chronic lymphocytic leukemia presented with a 3-day history of fatigue, dyspnea, fever, & a cough.

- Ceftriaxone, clarithromycin, and voriconazole was started, along with codeine 25 mg TID for cough.

- On day 4, the patient's level of consciousness rapidly deteriorated, and he became unresponsive. His last dose of codeine had been administered 12 hours earlier.

- Patient's pupils were miotic; no focal deficits were detected.
Example (NEJM 2004; 351:2827)

- The BUN & SCr were 45 mg/dl and 2 mg/dl, respectively; levels subsequently normalized with hydration.
- IV administration of naloxone (0.4 mg) that was repeated twice resulted in a dramatic improvement in pt's level of consciousness.
- With naloxone, consciousness was maintained and respiratory failure resolved. Two days after the acute event, the patient had recovered completely.
- Why did this occur?
Metabolic Pathways of Codeine Biotransformation.
Practice Pearls

- “Go low, go slow, go old”
- Know the drug therapy very, very well
  - Warfarin vs. DOACs
- Consider deprescribing of complex drug regimens
Practice Pearls

- Determine if dosage adjustments are recommended by manufacturer based on:
  - Hepatic/renal function
  - Data on use in “real world” older patients
  - PK/PD may not be known
- Start with lower dosages
- Monitor person more closely
Summary

- Aging is associated with important physiologic changes that alter PK/PD.
- Concomitant diseases, drugs, and other factors may also significantly influence PK/PD and patient outcomes.
- Altered PK/PD may decrease the likelihood of safe and effective drug therapy in older persons.
- Careful assessment of renal function is a key responsibility for health professionals in all practice settings.
Series aims to enhance geriatric competencies of healthcare providers and professionals serving older populations, particularly those with complex care needs, and includes five, topic-focused courses offered annually.

1. *Palliative Care and Hospice* – Course 1 (currently available on line)

2. *Stand Up and Stop Falls! Working Together to Prevent Falls in Older Adults* – Course 2 (April/May 2017)

3. *Optimal Pharmacotherapy* – Course 3 (May/June 2017)

4. *Cognitive Dysfunction* – Course 4 (June/July 2017)

5. *Mental, Social and Behavioral Health* – Course 5 (July/August 2017)

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- RIGEC will email nursing and social work certificates on Mondays. Healthcentric Advisors will email CME certificates on Mondays.

- For questions about CME certificates, please email Susan Midwood at smidwood@healthcentricadvisors.org

Thank you!!
Evaluation Link

https://www.surveymonkey.com/r/ZRSS532