Biology of Aging

Aging Changes That Impact Medication Management
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Faculty Disclosure
I have no relevant financial disclosures relative to the content of this presentation.
Learning Objectives

At the conclusion of this application-based activity, participants should be able to:

1. Recognize the physiological heterogeneity of the older adult population.
2. Recognize the spectrum of aging from healthy aging to frailty.
3. Compare and contrast age-related physiologic changes versus pathophysiologic changes in older adults.
4. Evaluate the impact of age-related pharmacokinetic/pharmacodynamic changes on drug disposition in older adults.
5. Apply the knowledge of physiologic changes associated with aging to the clinical use of medications, including PK/PD changes.

Audience Participation

How do you define “the aging population”?
The Aging Process

• Aging is a pattern of life changes that occurs as one grows older
• Gerontology is the study of individual and collective aging processes
  • Biological age
  • Psychological age
  • Social age
  • Legal age
  • Functional age
Is Aging Synonymous with Disease?

• Aspects of the aging process make us more vulnerable to illness and disease
  • However, no pathology is inevitable with age!

• Physical changes once attributed to aging are now recognized as being related to lifestyle choices

Normative Aging

• Series of time-dependent anatomic and physiologic changes that reduce physiologic reserve and functional capacity
  • Aging = reduced tissue/physiological function
  • Aging = increased susceptibility to disease
  • Aging = decreased resistance to stress
**Normative Biological Changes**

**VISION**
- Presbyopia occurs in the 40s and can be corrected with glasses

**HEARING**
- Subtle changes usually begin in the 40s and progress gradually with age
  - Loss of high-frequency hearing may decrease ability to recognize speech

**SMELL**
- Odor identification may be less efficient, likely due to environmental factors and olfactory receptors not being replaced as completely as younger adults
- Tinnitus may be the result of certain diseases or medications

**TASTE**
- Noticeable decrease in sense of taste is reported around age 60-70 as taste receptors change
- Dry mouth is the result of decreased saliva production

**TOUCH/SKIN**
- Research is limited, but changes in touch and skin receptors is thought to take place gradually. There may be some loss of receptors over time, so more stimulation may be required to elicit a response.

**Non-Normative Biological Changes**

Incidence of macular degeneration, glaucoma, and cataracts may increase with age, but none are considered normal aging.

Significant hearing loss occurs as a result of damage to ear structure.

Loss of smell (and likely taste) can occur as a result of upper respiratory infections, head trauma, nasal or sinus diseases.

Frailty

A clinical syndrome in which 3 or more of the following criteria are present:

- Unintentional weight loss (10 lbs in the past year)
- Self-reported exhaustion
- Weakness (grip strength)
- Slow walking speed
- Low physical activity

Frail older adults are at increased risk of falls, worsening mobility or ADL disability, hospitalization, and death.

Possible Trajectories of Physiologic Reserve During Aging

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal. In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In severe dementia, they cannot do personal care without help.
Audience Participation

Which pharmacokinetic parameter is LEAST affected by age-related physiological changes?

a) Absorption  
b) Distribution  
c) Metabolism  
d) Excretion
Audience Participation

Which benzodiazepines are “preferred” among older adults?

a) Lorazepam, oxazepam, temazepam
b) Diazepam, flurazepam, triazolam
c) Alprazolam, clonazepam, lorazepam
d) Clorazepam, midazolam, triazolam

Absorption

Physiological Change

• ↑ gastric pH
• ↓ gastric acid secretion
• ↓ gastrointestinal blood flow
• ↓ gastric surface area
• ↓ gastrointestinal motility

Pharmacokinetic Consequences

• Potential for delay in absorption, but no significant change in extent of absorption for most drugs
  • Exception: increased gastric pH → decreased absorption of calcium carbonate, increased risk of constipation

Absorption: Take-Home Message

- Most drugs are well-absorbed in the presence of age-related changes only

- Age-related changes as well as concurrent diseases result in increased variability in drug absorption

- Effects of aging on absorption from other sites of administration are poorly understood

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Distribution

<table>
<thead>
<tr>
<th>Physiologic Change</th>
<th>Volume of Distribution (Vd) Effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ body water</td>
<td>↓ Vd for hydrophilic drugs</td>
<td>ethanol, lithium</td>
</tr>
<tr>
<td>↓ lean body mass</td>
<td>↓ Vd for drugs that bind to muscle</td>
<td>digoxin</td>
</tr>
<tr>
<td>↑ fat stores</td>
<td>↑ Vd for lipophilic drugs</td>
<td>diazepam</td>
</tr>
<tr>
<td>↓ albumin</td>
<td>↑ % of unbound or free drug</td>
<td>valproic acid, phenytoin, warfarin</td>
</tr>
</tbody>
</table>
Distribution: Take-Home Message

• Distribution may be altered due to age-related physiologic changes and concurrent diseases

• Lipid-soluble drugs may show an increased volume of distribution while water-soluble drugs may show a decreased volume of distribution

• Age-related changes in protein binding do not generally result in clinically significant changes in drug therapy

Metabolism

Physiological Change
• ↓ hepatic blood flow
• ↓ hepatic mass
• ↓ CYP450 content

Pharmacokinetic Consequences
• Phase I metabolism may be impaired/prolonged
• ↔ Phase II metabolism in fit older adults
  • ↓ in frail older adults
  • (↓ first-pass metabolism)
### Metabolism

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I: oxidation, hydroxylation, dealkylation, reduction</td>
<td>Conversion to metabolites of lesser, equal, or greater</td>
<td>diazepam, quinidine, piroxicam, theophylline</td>
</tr>
<tr>
<td>Phase II: glucuronidation, conjugation, or acetylation</td>
<td>Conversion to inactive metabolites</td>
<td>lorazepam, oxazepam, temazepam</td>
</tr>
</tbody>
</table>

#### Metabolism: Take-Home Message

- For oxidatively metabolized drugs, doses should generally be reduced then adjusted based on patient response and tolerability

- Drugs metabolized exclusively by Phase II mechanisms are preferred

- Potential for significant drug interactions, particularly resulting from hepatic enzyme inhibition in patients on multiple medications, must be carefully considered
Excretion

Physiological Change
• ↓ renal blood flow
• ↓ glomerular filtration rate
• ↓ tubular secretion

Pharmacokinetic Consequences
• Renal elimination of drugs can be impaired, thus altering drug t½


Excretion

\[
Cl_{cr} = \frac{(140 - age) \times 62}{72 \times 1.3}
\]

Estimated CrCl
• Age 45 = 63 mL/min
• Age 65 = 50 mL/min
• Age 85 = 36 mL/min

• Digoxin
  • \( t\frac{1}{2} = 38-48 \) hours in patients with normal renal function
  • 69 hours on average in older adults

• Ranitidine
  • Usual treatment dose: 150 mg twice daily or 300 mg daily
  • \( CrCl < 50\text{mL/min} \rightarrow 150 \text{mg every 24 hours} \)
Excretion: Take-Home Message

• Decreased renal clearance of drugs is the most significant age-related change in PK, accounting for the majority of necessary dose adjustments

• Serum creatinine may be a poor predictor of renal function, especially in frail older adults

Pharmacodynamics

• Age-related changes in receptor responsiveness and homeostatic regulation may alter an older adult’s response to drug therapy
  • Changes in receptor number or affinity or changes in post-receptor response
  • Impairment of physiologic and homeostatic mechanisms
    • ↓ physiologic reserve
    • ↓ baseline performance
Drugs Whose Sensitivity is Altered with Advancing Age

- B-agonists (↓)
- B-blockers (↓)
- Benzodiazepines (↑)
- Calcium antagonists (↓↑)
- Dopaminergic agents (↑)
- Furosemide (↓)
- H₁-antihistamines (↑)
- Metoclopramide (↑)
- Neuroleptics (↑)
- Opioids (↑)
- Warfarin (↑)
- Vaccines (↓)

Pharmacodynamics

- Physiologic and homeostatic changes may affect drug responses, altering baseline performance and the ability to compensate for effects of medications
  - Medications can also contribute to geriatric syndromes

- Medications that act on the CNS and cardiovascular system are of particular concern
  - Potential for synergistic or additive effects from concurrent medication use exist
Clinical Pharmacology Paradigm

Drug → Pharmacokinetics → Pharmacodynamics → Efficacy

Pharmacokinetics: Concentration in the Circulation
- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamics: Drug Effect
- Drug-receptor interactions
- Concentration at receptors
- Homeostatic mechanisms

Efficacy: Desirable Therapeutic Outcome
- Compliance/adherence
- Disease characteristics