Pharmacokinetic and Pharmacodynamic Considerations in Geriatrics

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Disclosure

- The presenter has no conflicts of interest to disclose.
Learning Objectives

- Explain why it is important to understand the pharmacokinetics of drugs in geriatric patients.
- Evaluate the alterations in physiological factors that occurs with age.
- Analyze the effects of altered physiological factors on the absorption, distribution, metabolism, and elimination of drugs in geriatrics.
Learning Objectives

- Examine the effects of altered physiological factors on the independent and dependent pharmacokinetic parameters in geriatrics.
- Estimate the renal function of a geriatric patient by applying the Cockcroft and Gault equation.
Epidemiology

- Approximately 40 million people in the United States are over 65 years old
  - By 2030, elderly will account for 20% of population
  - By 2050, elderly will increase to 89 million people
- Those 85+ yrs are the fastest growing age group in the US population
# Physiological Changes in Elderly

## Body composition

<table>
<thead>
<tr>
<th>Physiological factor</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body water</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Body fat</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Muscle mass</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Serum albumin</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>$\alpha_1$-acid glycoprotein</td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>
Physiological Changes in Elderly

- Central Nervous System (CNS)
  - Alterations in cognition, changes in receptor sensitivities

- Cardiac System:
  - Decreased cardiac responsiveness to catecholamines
  - Decreased stroke volume and cardiac output
  - Thickening of walls of artery (atherosclerosis)
Physiological Changes in Elderly

- Gastrointestinal System
  - Decreased gastric acidity
  - Delayed gastric emptying
  - Decreased peristaltic response in esophagus
  - Decreased intestinal mobility
  - Decreased absorptive cells
Physiological Changes in Elderly

- Reflex system
  - Baroreceptor reflex sensitivity and responsiveness decrease

- Hepatic System
  - Reduced hepatic blood flow
  - Decreased first-pass metabolism
  - Decreased activity and production of metabolic enzymes
Physiological Changes in Elderly

- Renal System
  - Decreased GFR
  - Decreased renal blood flow
  - Decreased active tubular secretion

- Decreased muscle mass (sarcopenia)
  - Decreased SCr
  - Increased risk of falls
  - Reduced physical activity
  - Reduction in overall energy expenditure
PK Changes - Absorption

- Primarily a passive process in the small intestine
  - Rate of absorption may be reduced, resulting in delayed or lower peak serum levels
- Increase bioavailability for some drugs that are hepatically metabolized from first-pass effect (reduced)
- Transdermal absorption is variable
PK Changes - Absorption

- Example: Furosemide The extent of furosemide oral absorption is not changed, but the rate of absorption is slowed. Therefore the rate of active furosemide secretion into the urine does the reach critical levels (steep portion of the dose-response curve) to elicit a pharmacological response. Elderly patients may respond better to IV furosemide to avoid the variability created by slowed oral absorption.
PK Changes – Volume of Distribution

- Factors affecting drug distribution
  - Decreased
    - Lean body mass
    - Total body water
    - Serum albumin
    - Cardiac output
  - Increased
    - Total body fat
    - $\alpha_1$-acid glycoprotein
PK Changes – Protein Binding

- Example: Phenytoin Phenytoin has high protein binding – approximately 90%. As serum albumin decreases with age, the free fraction percentage of phenytoin may increase up to 18%. This leads to increased pharmacological and toxicology effects. Serum free phenytoin concentrations as well as serum albumin need to monitored in the geriatric population.
Clinical Example

- \( \left( \frac{[\text{Albumin}_{\text{Normal}}]}{[\text{Albumin}_{\text{Patient}}]} \right) \times [\text{Phenytoin}] = \text{Effective Level} \)

- \( \left( \frac{[4.4 \text{g/dL}]}{[3.0 \text{g/dL}]} \right) \times [10 \text{mcg/mL}] = 16.7 \text{mcg/mL} \)

- Essentially, in a patient with low albumin, a drawn level of 10.0mcg/mL “acts” like a level of 16.7mcg/mL
PK Changes – Metabolism

- Decreased hepatic blood flow by 45% between 25 to 65 years
- Decreased liver mass
- Decreased first-pass metabolism
  - Increased parent drug absorption
- Nutrition and comorbidities
## PK Changes – Metabolism

- Altered enzymatic activity

<table>
<thead>
<tr>
<th>Decreased</th>
<th>Decreased or Unchanged</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 1A2</td>
<td>CYP 2A</td>
<td>CYP 2D6</td>
</tr>
<tr>
<td>CYP 2C19</td>
<td>CYP 2C9</td>
<td></td>
</tr>
<tr>
<td>CYP 3A4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PK Changes – Metabolism

- Additional factors that may influence drug metabolism:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Induction</td>
</tr>
<tr>
<td>Diet</td>
<td>Variable</td>
</tr>
<tr>
<td>Drugs</td>
<td>Induction/Inhibition</td>
</tr>
<tr>
<td>Frailty</td>
<td>Inhibition</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Inhibition, if severe</td>
</tr>
<tr>
<td>Smoking</td>
<td>Induction</td>
</tr>
</tbody>
</table>
PK Changes – Elimination

- Elimination of drugs primarily occurs at the kidneys
- Renal perfusion can decrease 40-50% from between the ages of 25 to 65 years
  - Compounded by arteriosclerotic changes and decreased cardiac output
- Kidney mass decreases 20-25% from the ages of 30 to 80 years
PK Changes – Elimination

- Net effect:
  - Decreased clearance of drugs (most dramatic change)
  - 50% decline in renal clearance of drugs by age of 75-80yrs old
  - Examples: famotidine, glyburide, atenolol, benazepril, levofloxacin
PK Changes – Elimination

- Creatinine is a byproduct of muscle metabolism
  - Creatinine is freely-filtered at glomerulus, not actively secreted, and not reabsorbed by kidneys
  - Freely distributed throughout all body tissue
  - May be utilized as an estimate of renal function (estimated glomerular filtration rate; eGFR)
  - For drugs that are eliminated renally, drug dosing may be reliant on creatinine clearance ($\text{Cl}_\text{Cr}$)
Rounding of Serum Creatinine

- Estimation of clearance: Cockcroft and Gault equation

\[
Cl_{Cr} = \frac{(140 - age) \times IBW}{72 \times SCr} \times (0.85 \text{ if female})
\]

- Some patients who are “frail” or exhibit muscle wasting will have SCr less than 1.0mg/dL
  - Low SCr will generate large \( Cl_{Cr} \) as calculated by Cockcroft-Gault equation
Rounding of Serum Creatinine

- Case Study: YM is a 68yo male, 5’10, Actual BW = 68kg (IBW = 73kg), SCr = 0.6mg/dL.

- What is the Cl_{Cr} if you use the actual SCr vs rounded SCr?
  - Actual SCr: \((140-68) \times 68 / (72 \times 0.6) = 113\text{mL/min}\)
  - Rounded SCr: \((140-68) \times 68 / (72 \times 1.0) = 68\text{mL/min}\)
Rounding of Serum Creatinine

- In elderly patients with SCr < 1.0 mg/dL, many clinicians will round up to SCr = 1.0 mg/dL.
  - This will reduce the Cl\textsubscript{Cr} as calculated from Cockcroft and Gault (113 mL/min vs 68 mL/min)
  - Lower Cl\textsubscript{Cr} could lead to smaller, more conservative doses
Rounding of Serum Creatinine

- Studies performed on the accuracy and performance of rounding low SCr in elderly
  - Rounding of low SCr to 1.0mg/dL resulted in substantial underestimation of $C_l_{Cr}^{1,2}$ and correct aminoglycoside dose
  - Meta-analysis demonstrated actual SCr most closely estimated measured $C_l_{Cr}^{3}$

Rounding of Serum Creatinine

- Studies concluded that rounding SCr did not improve accuracy or bias.\textsuperscript{1,2,3}

- Rounding of SCr in elderly patients is subjective and should be performed on a case-by-case basis

Pharmacodynamics

- Changes in drug response largely due to physiological changes with aging
- Pharmacological effects may be enhanced or diminished
  - Similar doses may elicit greater response
  - Dosing range for elderly may be smaller
Pharmacodynamics
Clinical Pearls

- Benzodiazepines (BZD)
  - Increased $V_d$ results in increased $t_{1/2}$ – use short-acting benzodiazepines to avoid oversedation
  - Receptor sensitivity increases with age – increased pharmacological and toxicological effects
    - Short-acting BZD (lorazepam, oxazepam, alprazolam, temazepam, and triazolam) preferred with dose reduction
    - Long-acting BZD (chlordiazepoxide, diazepam, halazepam, and chlorazepate) should be avoided
Clinical Pearls

Zolpidem

- $C_{p_{\text{max}}}$, $t_{\text{max}}$, and AUC are increased
- Initiate with half of regular recommended dose in elderly
  - FDA recommends reduced dose in females
- Receptor sensitivity increases with age – increased pharmacological and toxicological effects
Clinical Pearls

- **Eszopiclone**
  - **Pharmacokinetics**
    - AUC increased by 41% in older adults
    - Mean half-life increased to 9 hours
  - **Maximum recommended dose**: 2mg
  - **Pharmacodynamics**
    - Age-associated changes in the CNS promote adverse effects
  - No gender-based PK differences
Clinical Pearls

- Aminoglycosides (gentamicin, tobramycin, amikacin)
  - Decreased $V_d$, loading doses may need to be adjusted
  - Decreased clearance, adjust maintenance doses and dosing interval according to renal function and half-life
  - Dosing – elderly patients with high SCr may be at higher risk for toxicity due to prolonged higher serum levels
Clinical Pearls

- Nitrofurantoin
  - Antibiotic commonly used for urinary tract infections (UTI) – decreased renal clearance results in lower concentration of antibiotic in urine
  - Risk for systemic accumulation increases with $\text{Cl}_{\text{Cr}} < 60\text{mL/min}$
Clinical Pearls

- Vancomycin
  - Increased $V_d$, loading doses may need to be adjusted
  - Decreased clearance, adjust maintenance doses and dosing interval according to renal function and half-life
Clinical Pearls

- **Metformin (FDA, 2016)**
  - Contraindicated if $\text{Cl}_{\text{Cr}} < 30 \text{mL}$ as of 4/8/2016
  - Previous: Contraindicated in males $\text{SCr} \geq 1.5 \text{mg/dL}$, females $\text{SCr} \geq 1.4 \text{mg/dL}$
Clinical Pearls

- Glyburide has longer duration and renally excreted
  - Risk of severe prolonged hypoglycemia
  - Recommend to dose conservatively or switch to glipizide
Clinical Pearls

- **Incretin Mimetics**
  - No age-related PK changes; dosing based on $\text{Cl}_{\text{Cr}}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cl_{\text{Cr}}</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Exenatide</td>
<td>&lt;30mL/min</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>&lt;50mL/min</td>
<td>Use with caution</td>
</tr>
</tbody>
</table>
### Clinical Pearls

- **DPP-IV Inhibitors**
  - No age-related PK changes; dosing based on $\text{Cl}_{\text{Cr}}$

<table>
<thead>
<tr>
<th></th>
<th>$\text{Cl}_{\text{Cr}}$</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>30-59mL/min, &lt;30mL/min</td>
<td>12.5mg PO daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.25mg PO daily</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>&lt;50mL/min</td>
<td>2.5mg PO daily</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>30-50mL/min, &lt;30mL/min</td>
<td>50mg PO daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25mg PO daily</td>
</tr>
</tbody>
</table>
Clinical Pearls

- **SGLT-2 Inhibitors**
  - No age-related PK changes; dosing based on eGFR

<table>
<thead>
<tr>
<th>Drug</th>
<th>eGFR /1.73m²</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>45-59mL/min</td>
<td>100mg/day</td>
</tr>
<tr>
<td></td>
<td>&lt;45mL/min</td>
<td>Do not use</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>&lt;60mL/min</td>
<td>Do not use</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>&lt;45mL/min</td>
<td>Do not use</td>
</tr>
</tbody>
</table>
Clinical Pearls

- **Digoxin**
  - Decreased $V_d$, loading doses may need to be adjusted
  - Decreased clearance, adjust maintenance doses and dosing interval according to renal function and half-life

- **ACE-Inhibitors**
  - Moderate to severe renal dysfunction ($\text{Cl}_{\text{Cr}}<30\text{mL/min}$), most ACE inhibitors require dose reduction
  - Need to watch for potassium
Clinical Pearls

- Beta-Blockers
  - Pharmacokinetics
    - Bioavailability of some agents may be increased due to reduced hepatic first-pass metabolism
    - Clearance reduced and half-life prolonged
  - Pharmacodynamics
    - Decreased β-receptor response may increase adverse event risk
Clinical Pearls

Warfarin

- Elderly patients tend to be more “sensitive” to warfarin, requiring dosage adjustment
  - Doses usually titrated to effect (INR)
- Age-associated changes in skin, vascular integrity promotes easy bruising
- Lower starting doses
- Dose adjustment every 5-7 days
Clinical Pearls

- H2-antagonists (cimetidine, ranitidine, famotidine, nizatidine)
  - Adjust according to renal function
  - Cimetidine involved in multiple drug interactions via CYP1A2, 2C19, 2D6, and 3A4
Conclusion

- Physiological changes associated with aging may affect various PK processes of absorption, distribution, metabolism, and elimination.
- Dosing adjustments are frequently necessarily – “go low, go slow”.
- Elderly patients may be more sensitive to certain medications and require close monitoring and dose adjustments.
References

References

References

THANK YOU! QUESTIONS?
Test Questions

If a patient has a SCr < 1.0mg/dL, rounding the SCr up to 1.0mg/dL would

A. Increase $Cl_{Cr}$
B. Decrease $Cl_{Cr}$
C. Have no effect
D. Not enough information
Test Questions

The new contraindication for metformin is:

A. SCr ≥ 1.5mg/dL for males
B. SCr ≥ 1.4mg/dL for females
C. Cl_{Cr} < 45mL/min
D. Cl_{Cr} < 30mL/min
It is recommended to reduce the starting dose of zolpidem in which of the following patient populations?

A. Elderly patients and females
B. Elderly patients and males
C. Young adults
D. Patients with sleep apnea
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