Prescribing and Pharmacokinetic Considerations in the Elderly

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OBJECTIVES

At the conclusion of the lecture the student shall be able to:

- Describe the effects of aging on pharmacokinetic parameters (absorption, distribution, metabolism, and elimination)
- Describe the effects of aging on pharmacodynamic parameters
- Discuss basic principles of prescribing for older patients to avoid adverse drug effects
- Identify potentially inappropriate medications in a given elderly patient based on the Beers’ criteria
Why are geriatric pharmacokinetics important?

- Persons aged 65 and older are prescribed the highest proportion of medications in relation to their percentage of the U.S. population

  - Now, 13% of total population buy 33% of all prescription drugs
  - By 2040, 25% of total population will buy 50% of all prescription drugs
Why are geriatric pharmacokinetics important?

- Increased risk of adverse drug reactions
  - Multiple medications
    - >20% of elderly use 5 or more medications
    - Increased frequency of drug-drug interactions
    - Decreased medication adherence
  - Multiple comorbidities
  - Age-related changes in drug pharmacokinetics
  - Age-related changes in drug pharmacodynamics
The Burden of Injuries from Medications

- ADEs are responsible for 5% to 28% of acute geriatric hospital admissions
  - ADEs occur in 35% of community-dwelling elderly persons
  - ADEs incidence: 26/1000 hospital beds
  - In nursing homes, $1.33 spent on ADEs for every $1.00 spent on medications
RISK FACTORS FOR ADEs

- 6 or more concurrent chronic conditions
- 12 or more doses of drugs / day
- 9 or more medications
- Prior adverse drug reaction
- Low body weight or body mass index
- Age 85 or older
- Estimated CrCl < 50 mL / min
Principles of prescribing for older patients: The Basics

• Start with a low dose

• Titrate upward slowly, as tolerated by the patient

• Avoid starting 2 drugs at the same time
Before Starting a New Medication, Ask:

- Is this medication necessary?
- What are the therapeutic end points?
- Do the benefits outweigh the risks?
- Is it used to treat effects of another drug?
- Could 1 drug be used to treat 2 conditions?
- Could it interact with diseases, other drugs?
- Does patient know what it’s for, how to take it, and what ADEs to look for?
PHARMACOKINETICS

Absorption

Distribution

Metabolism

Elimination
Aging and Absorption

- Clinical significance is not well characterized
  - Most drugs absorbed through passive diffusion in the proximal small bowel

- Exception: levodopa
  - Threefold increase in bioavailability due to reduced activity dopa-decarboxylase in the stomach wall
Absorption

- **Alterations in GI function**
  - **Decreased gastric parietal cell function**
    - Decrease in secretion of hydrochloric acid
  - **Increase in gastric pH**
    - Ex: tetracycline, Fe, ketoconazole

- **Decreased rate of gastric emptying**
  - Ex: anticholinergics, opiates, Fe, anticonvulsants

- **Drug-drug interactions**
  - Divalent cations (calcium, magnesium, iron) and fluoroquinolones (e.g., ciprofloxacin)
Absorption

- Topical absorption (patches, creams, ointments, etc.)
  - Thinning and reduction of absorptive surface
    - Skin atrophy and decreased fat content
      » Reduction in vascular network and risk of contact dermatitis
Effects of aging on volume of distribution (Vd)

- Depends mostly on physiochemical properties of individual medications

\[ t_{1/2} = \frac{0.693 \times Vd}{Cl} \]
Distribution

- ▼ body water (10-15%) → lower Vd for hydrophilic drugs
  - Ex: warfarin, digoxin, lithium, cimetidine, APAP, ETOH

- ▼ lean body mass → lower Vd for drugs that bind to muscle

- ▲ fat stores → higher Vd for lipophilic drugs
  - Ex: diazepam, lidocaine, TCAs, propranolol
Distribution
Protein Binding

- **Decreased serum albumin**
  - 10 to 20% in hospitalized or poorly nourished pt.
  - Increase in unbound fraction of highly protein bound acidic drugs
  - Monitor drug levels—free phenytoin level with low albumin
    - Ex: warfarin, phenytoin, naproxen

- **Increased α-1 acid glycoprotein**
  - Decrease in unbound fraction of highly protein bound basic drugs
    - Ex: lidocaine, propranolol, imipramine
The liver is the most common site of drug metabolism

Metabolic clearance of a drug by the liver may be reduced because …

Decrease in liver blood flow
- 40 to 45% with aging, related to cardiac function
- Increase in bioavailability
- Decreased 1st pass effect = more parent drug
  - Reduce initial dose, then titrate

Decrease in liver size
- 20 to 50% decrease in absolute weight up to age 80
- Reduction of total amount of metabolizing enzymes
- Leads to decrease in Cl and increase in $t_{1/2}$
- Start with lower dosage
- Caution with toxic metabolites
  - Ex: meperidine and propoxyphene
Other Factors that Affect Drug Metabolism

- Gender
- Hepatic congestion from heart failure
- Smoking
Elimination

- Most drugs exit body via kidney
- Reduced elimination $\rightarrow$ drug accumulation and toxicity
- Aging and common geriatric disorders can impair kidney function
The Effects of Aging on the Kidney

- ↓ kidney size
- ↓ renal blood flow
  - ~1%/year after age 50
- ↓ number of functioning nephrons
- ↓ renal tubular secretion

Result: Lower glomerular filtration rate

- ~35% in healthy individuals between ages 20 and 90
- Accumulation → increased risk of toxicity
  - Ex: lithium, aminoglycosides, captopril, NSAIDs
Serum Creatinine does NOT reflect Creatinine Clearance

- ↓ lean body mass → lower creatinine production
  and
- ↓ glomerular filtration rate (GFR)

Result: In older persons, serum creatinine stays in normal range, masking change in creatinine clearance (CrCl)
How to Calculate Creatinine Clearance

• **Measure:**
  ✓ Time-consuming to be accurate
  ✓ Requires 24-h urine collection
  ✓ 8-h collection may be accurate but not widely accepted

• **Estimate:**
  ✓ Cockroft and Gault equation
  ✓ MDRD
Cockroft and Gault Equation

(Ideal weight in kg) \( (140 - \text{age}) \) 
\[ \frac{\text{serum creatinine in mg/dL}}{72} \] 
\[ \times \ (0.85 \text{ if female}) \]
Pharmacodynamics

Definition

• Time course and intensity of pharmacologic effect of a drug

   Impairment varies considerably from person to person

   All organ systems are affected

   Kidneys, liver, GI, CNS, CV, GU
Altered Pharmacodynamic Mechanisms

- Change in receptor numbers
- Change in receptor affinity
- Postreceptor alterations
- Age-related impairment of homeostatic mechanisms
CNS

- Changes are significant, yet idiosyncratic
  - Decrease in weight and volume of brain
  - Alterations in cognition

- Increased sensitivity to medications
  - Ex: benzodiazepines, opioids, anticholinergics, NSAIDs
CNS

- Cholinergic blockade results in
  - Sedation, confusion, and reduced ability to recall
    - Ex: TCAs, diphenhydramine, antispasmodics, antipsychotics

- Benzodiazepines can cause severe CNS depression
  - Leads to falls and hip fractures
  - Use caution and small dosages
Cardiovascular

- Decreased baroreceptor responsiveness
  - Results in orthostatic hypotension
    - Ex: Antihypertensives—use caution and counseling
GU

- Urinary incontinence
  - 15 to 30% of community-dwellers
  - 50% of nursing home residents
  - Enlarged prostate, urine retention
    - Ex: anticholinergics
Inappropriate Medication Use in Older Adults (Beers Criteria update)

- 48 medications or classes to avoid in older adults
- 20 diseases/conditions and medications to avoid in older adults with these diseases
- “Medications to be used with caution in the elderly: a statewide clinical recommendation on potentially inappropriate medications”
## Inappropriate Drug Therapy based on Beers’ Criteria

<table>
<thead>
<tr>
<th>Authors</th>
<th>Setting</th>
<th>Prevalence of Inappropriate Prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goulding MR 2004</td>
<td>Ambulatory care visits</td>
<td>7.8% of visits</td>
</tr>
<tr>
<td>Zhan et al. 2001</td>
<td>Community dwelling elderly</td>
<td>21.3% of patients</td>
</tr>
<tr>
<td>Simon SR, et al. 2005</td>
<td>Elderly in managed care</td>
<td>28.8% of patients</td>
</tr>
<tr>
<td>Golden et al. 1999</td>
<td>Nursing home-eligible</td>
<td>39.7% of patients</td>
</tr>
<tr>
<td>NM Medicare Advantage plans 2009</td>
<td>New Mexico Medicare patients</td>
<td>21.5% of patients</td>
</tr>
</tbody>
</table>
Beers’ Criteria: Independent of Diagnosis
Analgesics

- Meperidine (long t$_{1/2}$ metabolite, CNS)
- Non-steroidal anti-inflammatory drugs
  - Indomethacin (CNS)
  - Ketorolac-immediate and long-term use (GI bleeds)*
  - Non-COX selective NSAIDs, longer t$_{1/2}$-long-term use (GI bleeds, renal failure)*
- Propoxyphene
- Pentazocine (CNS)
Beers’ Criteria: Independent of Diagnosis
Psychiatric

- **Antidepressants**
  - Amitriptyline/doxepin (anticholinergic)
  - Daily fluoxetine (CNS)*

- **Anxiolytics**
  - Long-acting benzodiazepines-chlordiazepoxide, flurazepam (sedation/fractures)
  - Doses of short-acting benzodiazepines
  - Meprobamate (addiction/sedation)

- **Antipsychotics**
  - Thioridazine (CNS/EPS)*
  - Mesoridazine (CNS/EPS)*
Beers’ Criteria: Independent of Diagnosis
Cardiovascular

- Ticlopidine (no better than aspirin)
- Disopyramide (negative inotrope/anticholinergic)
- Amiodarone (QT interval/torsades de pointes)*
- Methyldopa (bradycardia/depression)
- Clonidine (CNS/orthostatic hypotension)*
- Doxazosin (hypotension/dry mouth)*
- Short-acting nifedipine (hypotension/constipation)*
- Ethacrynic acid (HTN, fluid imbalances)*
Beers’ Criteria: Independent of Diagnosis

- **Antihistamines (anticholinergic)**
  - Diphenhydramine (confusion/sedation)
  - Chlorpheniramine
  - Promethazine
  - Hydroxyzine

- **Stimulant laxatives, long term use: e.g., bisacodyl (bowel dysfunction)**

- **Cimetidine (CNS, confusion)** *

- **Chlorpropamid (hypoglycemia/SIADH)**
Beers Criteria
Considering Diagnosis

- Heart failure-disopyramide (negative inotropic effect)
- Gastric or duodenal ulcers-NSAIDs and aspirin >325 mg (exacerbate existing ulcers or produce new ulcers)
- Epilepsy-clozapine, chlorpromazine (may lower seizure threshold)
- Insomnia-decongestants, theophylline, methylphenidate (CNS stimulants)
Beers Criteria
Considering Diagnosis

- Depression-long-term benzodiazepines (exacerbate depression)*
- Syncope or falls-TCAs and short to intermed acting benzodiazepines (may produce syncope/additional falls)*
- Chronic constipation-CCBs, anticholinergics, TCAs
Alternatives to Beers criteria

STOPP and START Criteria

- Screening Tool of Older Persons’ Prescriptions (STOPP)
- Screening Tool to Alert doctors to Right Treatment (START)

Conclusions

- Age alters pharmacokinetics (drug absorption, distribution, metabolism, and elimination)
- Age alters pharmacodynamics
- ADEs are common among older patients
- Successful drug therapy means:
  - Choosing the correct dosage of the correct drug for the condition and individual patient
  - Monitoring the therapy


