Pharmacotherapy in the Elderly

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Percentage of population with prescription and number of medication per individual increase with age
Definitions

• Pharmacology:
  • *pharmakon* = drug
  • *logos* = discourse
  • study of the fate and actions of drugs

  – Pharmacokinetics
    • study of time course of drug concentration and the factors affecting it

  – Pharmacodynamics
    • study of the mechanisms of drug action
**Pharmacological Principles**

- pharmacological agents work via high affinity binding to their cellular targets (receptors)
- agonist binding to receptors initiates physiological functions
- antagonist binding to receptors blocks agonists from gaining access
- partial agonist acts as an antagonist in the presence of a true agonist
Pharmacokinetic Factors

- Solubility
- Therapeutic window
- Adverse drug reactions
Physiological changes with age affecting pharmacokinetics

- decreased ratio of lean body mass
- decreased levels of serum albumin
- decreased liver function
- decreased renal function
Pharmacokinetics: absorption
Drug absorption changes in the elderly

*(Table 23.2)*

Gastrointestinal system (rarely clinically significant)

- acid production generally unchanged
- drug-drug interaction may alter absorption
- splanchnic blood flow decreases (with little effect on drug absorption)
Pharmacokinetics: distribution

- Distribution: affects the concentration of drug available at the target
- Hydrophilic vs. lipophilic drug
- Protein binding
- \( C = \frac{D}{V_d} \)
  - \( C \), concentration
  - \( D \), dosage
  - \( V_d \), volume of distribution

Diagram:
- Free drug in circulation
- Plasma protein binding
- Tissue storage (fat or muscle)
- Target site availability
- Absorption
- Biotransformation
- Elimination
Drug distribution changes in the elderly

*(Table 23.2)*

Fluid and tissue compartments

- decrease in total body water
- increase in fat compartment
- decrease in muscle mass

Plasma drug-binding proteins (rarely clinically significant)

- decrease in serum albumin levels
- no change in $\alpha$-acid glycoprotein levels
Pharmacokinetics: drug metabolism

Phase 1
Activation (some)
No change (some)
Inactivation (most)

Phase 2
Inactivation (almost all)

DRUG

Oxidation, Reduction, and/or Hydrolysis Products

Synthetic or Conjugation Products
Pharmacokinetics: biotransformation

Enzymatic reactions preparing drugs for elimination by the body

• Phase I reactions:
  – cytochrome P\textsubscript{450} enzymes
  – genetically variable
  – highly inducible enzyme expression

• Phase II reactions
  – conjugation: addition of small chemical groups to increase solubility of pharmacological agents
Drug metabolism changes in the elderly  
*(Table 23.2)*

Liver

- decrease in hepatic blood flow often associated with decreased First Pass Effect
- Phase I metabolism decreased
- Phase II metabolism generally preserved
Pharmacokinetics: elimination

- Elimination: removal of drug from the body by excretion
- Renal functions:
  - glomerular filtration
  - tubular secretion
- Other minor pathways of elimination:
  - feces
  - breath
  - sweat
  - saliva
Drug elimination changes in the elderly

Table 23.2

Decreased renal functions

- decreased blood flow to the kidneys
- decreased glomerular filtration
- decreased tubular secretion
- decline in creatinine clearance
Pharmacodynamics

- Study of the interaction between a pharmacological agent and its target tissue
- Study of the mechanism, intensity, peak and duration of a drug’s physiological actions
Physiological changes in elderly patients affecting pharmacodynamics

Target organ physiological changes
• increased sensitivity to pharmacological agents
• decreased desirable effects of pharmacotherapy
• increased adverse effects

Homeostasis changes
• decreased capacity to respond to physiological challenges and the adverse side effects of drug therapy
  (eg., orthostatic hypotension)
Adverse Drug Reactions

The elderly are 2-3 times more at risk for adverse drug reactions due to:

1. reduced stature
2. reduced renal and hepatic functions
3. cumulative insults to the body (e.g., disease, diet, drug abuse)
4. multiple and potent medications
5. altered pharmacokinetics
6. noncompliance
ADR: Anticoagulants

- elderly patients are more sensitive to the effects of anticoagulants
- Pharmacodynamic changes: vitamin K-dependent clotting factors deficiency
- Pharmacokinetic changes: anticoagulants such as warfarin have a very narrow therapeutic window and are highly protein bound
- drug interactions (e.g., phenytoin)
- adverse effect: excessive internal bleeding
- Frequent monitoring by primary care physician
ADR: NSAIDs

• Non-Steroidal Anti-Inflammatory Drugs are frequently prescribed in the elderly patients
• pronounced adverse gastrointestinal side effects
• other adverse drug reactions in the kidney and CNS have also been associated with chronic NSAID therapy in the elderly
• Alternate therapies:
  – acetaminophen (Tylenol) for analgesia
  – new COX-2 inhibitors for anti-inflammatory actions
ADR: Cardiovascular Agents

- congestive heart failure is a common age-related condition
- digoxin (isolated from the foxglove plant) used to be the drug of choice for congestive heart failure
  - drug elimination is reduced in the elderly; effective dose is variable
  - often worsens cardiac symptoms
- replaced by newer therapeutic agents: beta-adrenergic receptor blocker and angiotensin-converting enzyme inhibitors
Commonly used medications best avoided in the elderly

(Table 23.4)

- **Anticholinergic preparations**
  - diphenhydramine (*Benadryl*)
  - amitriptyline (*Elavil*)
  - oxybutynin (*Ditropan*)
  - doxepin (*Sinequan*)
  - dicyclomine (*Bentyl*)

- **Benzodiazepines with active metabolites**
  - diazepam (*Valium*)
  - chlorodiazepoxide (*Librium*)
  - flurazepam (*Dalmane*)

- **Central acting CNS agents**
  - alpha methyldopa (*Aldomet*)
  - clonidine (*Catapres*)

- **Analgesics**
  - propoxyphene (*Darvon*)
  - medperidine (*Demerol*)
  - indomethacin (*Indocin*)
Common problems of drug administration in the elderly

• reduced homeostasis
  – decreased renal and hepatic functions
  – increased target organ sensitivity

• polypharmacy
  – increased chance of adverse drug reactions

• lack of available data
  – fewer clinical trials on elderly populations

• non-compliance
Considerations for pharmacotherapy in the elderly

• Is drug therapy required?
• choice of appropriate drug and preparation
• dosage regimen to accommodate changes in physiology
• detailed monitoring and periodic re-evaluation of drug therapy
• clear and simple medication instructions

Figure 1. Effects of medication reduction on hospitalization and death rates.
Summary

- changes in the physiology of the elderly dictate responses to drug therapy
- pharmacokinetic changes affect the effective concentration of drug in the body
- pharmacodynamic changes affect the body’s response to the drug therapy
- adverse drug reactions are more common in the elderly and can be avoided with better primary care