



Pharmacokinetic and Pharmacodynamic Changes in Elderly

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Short version of talk

Absorption	Distribution	Metabolism
↓ Amount of saliva	↓ Cardiac output	↓ Microsomal hepatic oxidation
↑ Gastric pH	↑ Peripheral vascular resistance	↓ Clearance
↓ Gastric acid secretion	↑ Renal blood flow	↑ Steady-state levels
↑ Gastric emptying time	↓ Hepatic blood flow	↑ Half-lives
↓ Gastrointestinal surface area	↓ Body water	↑ Levels of active metabolites
↓ Gastrointestinal motility	↑ Body fat tissue	↓ First-pass metabolism
↓ Active transport mechanism	↑ Volume of distribution for lipid-soluble drugs	
↓ Gastric dopa	↓ Volume of distribution for water-soluble drugs	
↓ Decarboxylase	↓ Serum albumin levels	



Any Questions?



Pharmacokinetic changes
= changes in drug concentrations

- Absorption
- Distribution
- Metabolism/Elimination



Absorption changes

- ↓ Amount of saliva
- ↑ Gastric pH
- ↓ Gastric acid secretion
- ↑ Gastric emptying time
- ↓ Gastrointestinal surface area
- ↓ Gastrointestinal motility
- ↓ Active transport mechanism
- ↓ Gastric dopa
- ↓ Decarboxylase

→ Summary is delay in absorption of medications



Distribution changes

- Changes in body composition:
 - Decreased body water
 - Relative increase in body fat
- reduced volume of distribution for water soluble medications, and converse for fat soluble
- Reduced protein binding



→ Only alters loading doses

→ Phenytoin drug levels



Hepatic metabolism changes

- There are age related reductions in hepatic clearance
- There is no simple method of calculating hepatic clearance capacity

IMPORTANT? ✓

For most hepatically cleared drugs concentrations approximately double compared to younger controls

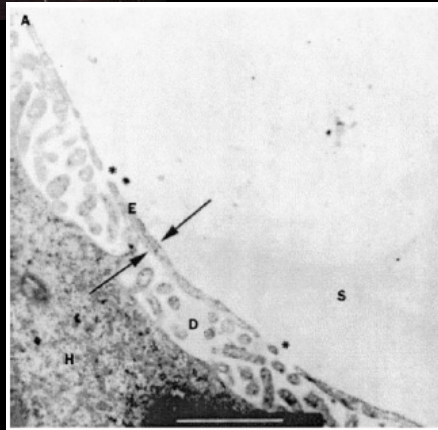


Mechanism of reduced hepatic clearance

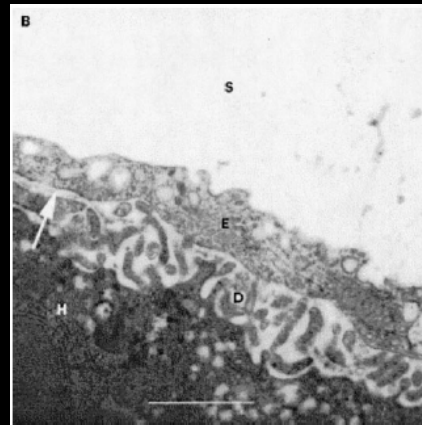
- Reduced liver size
- Reduced liver blood flow
- CYP activity is maintained (!!!)
 - However see sinusoidal fibrosis which may limit oxygen and drug exposure to hepatocytes
 - reduction in oxidation activity
- Conjugation appears to be maintained



Sinusoidal changes



Young rat



Older rat

LeCouteur et al 2001



Renal elimination changes

- Age related decline in renal blood flow, renal tubular clearance, and creatinine clearance
- Drugs can be filtered, secreted, or reabsorbed (passive or active)
 - ➔ Regardless of mechanism, calculated creatinine clearance is reliable method of estimating renal clearance
 - ➔ Creatinine IS NOT!!
 - ➔ MDRD or eGFR IS NOT!!



Impact of clearance changes

- Lower clearance = higher steady state concentration for same dose
- Particularly for high first pass drugs when administered orally
 - current anti-epileptics do not fall into this category
 - Other drugs SSRI's, atypical antipsychotics, morphine



Impact of clearance changes

- Longer half life
 - Longer to steady state and maximum steady-state concentration eg may occur after hospitalisation
 - Slower offset of effect when dose reduced or ceased
 - Longer period between dosage adjustment



Summary of pharmacokinetic changes

- Slower absorption and longer onset of maximal effect
- Water soluble drugs need smaller loading doses
- Smaller doses for same concentration
- Longer half lives
- Longer period of time between dose alteration



Start low, go slow!!!



Specific examples: Clearance changes

- Renally cleared drugs:
 - Gabapentin
 - Pregabalin
 - Levetiracetam
 - Vigabatrin
 - Topiramate (~80%)
- ➔ Dosage alteration in renal dysfunction



Specific examples: Clearance changes

- Hepatic oxidation:
 - Carbamazepine
 - Phenytoin
 - Valproate
 - Tiagabine
 - Benzodiazepines, barbiturates
- ➔ Clearance will be reduced in elderly
- Lamotrigine undergoes conjugation hence clearance not changed



Phenytoin concentrations

- Unbound (active) fraction 10% but total concentration measured
- Unbound fraction increases with
 - Aging
 - Hypoalbuminaemia
 - Chronic renal failure
- ➔ In elderly, a particular concentration equivalent to higher level in younger person due to greater unbound fraction



Pharmacodynamic changes

= Changes in drug effect at same concentrations



Many alterations described with aging

- Very complex area with extensive literature (often *in vitro!*)
- Include changes in:
 - Transmitters
 - Receptors
 - Signal-transduction
 - Homeostatic mechanisms
- Most of research in cardiovascular area



Pharmacodynamic Changes

- In general elderly more sensitive to medications
 - May need lower concentration of antiepileptic for efficacy (eg carbamazepine, valproate-Ramsay *et al* 1994)
 - Also have more adverse reactions



Pharmacodynamic Changes

- Due to alterations in physiology with aging or disease, may not have as much reserve to counteract effects of medications
 - Eg weight loss topiramate
 - Hyponatremia with oxcarbazepine, carbamazepine
 - Ataxia
 - Osteomalacia with hepatic inducers (phenytoin, carbamazepine, *and valproate*)



Other changes with aging

- Social isolation
- Dexterity changes
- Hearing problems
- Visual problems
- Intellectual changes
- Polypharmacy
- Financial difficulties

Less influence on prescribing but greater influence on
Quality Use of Medicines



Summary

- Start low
- Go slow
- Think outside the square
 - Compliance
 - Social, cultural, financial issues
 - Other comorbidities