Age related changes in kinetics and dynamics

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The relevance
The Time Span.

A great deal of treatment that is given to the young and middle aged is intended to prevent troubles in the distant future and some nuisance in the present may be accepted to obtain this end. The rigid control of hypertension and diabetes are examples. It is of course obvious that old people have no distant future, yet they are often continued on treatment which, however correct it might have been, can no longer benefit them.
Prescribing trends

Prescriptions per capita

Source: DOH, 1998
Terminology

**Pharmacodynamics:**

φαρµακον = medicine

δυναµις = power

**Pharmacokinetics:**

φαρµακον = medicine

κινετικον = movement
Pharmacokinetics in elderly patients

Renal function

- Reduced glomerular filtration
  - Approximately 20 - 50% reduction in GFR
  - Important for drugs predominantly renally excreted
    eg digoxin, lithium, aminogycosides
- Reduced tubular secretion
  - Less important and less well documented
- Therapeutic implications:
  - Reduce dose for once daily regimens
  - Reduce dose interval
Pharmacokinetics in elderly patients

**Hepatic function**

- Reduced liver volume (cf children)
  - up to 30% reduction
- Reduced liver blood flow
- Reduced enzyme activity (frail elderly)
- Reduced serum proteins (frail elderly)
  - Reduced protein binding
  - $\uparrow V_d$
Pharmacokinetics in elderly patients

Body content

- Physiology
  - Increased proportion of body fat
  - Decreased proportion of body water

- Implications
  - $\uparrow$ Vd of lipid soluble drugs
  - $\downarrow$ Vd of water soluble drugs

NB: $t_{1/2} \propto \frac{Vd}{CL}$
Pharmacokinetics in elderly patients

- Reduced glomerular filtration
- Reduced tubular secretion
- Reduced liver volume (cf children)
- Increased proportion of body fat
- Reduced enzyme activity (frail elderly)
- Reduced protein binding (↑Vd)(frail elderly)
- Reduced liver blood flow (↓clearance)
Theophylline clearance and age
Theophylline clearance and age

Theophylline clearance (ml/min/kg CBW)

Lower    Middle   Upper

(age range 20 - 87 years)

Jackson et al 1985
Ibuprofen

Age associated ↓ intrinsic CL of S ibuprofen
### Disease states

- **Migraine**
  - ↓ rate of absorption

- **Renal failure**
  - ↓ renal CL
  - ↓ protein binding
  - ± Na and H₂O retention (↑ V → ↑ t½)

- **Cardiac failure**
  - Na and H₂O retention
  - Hepatic congestion (↓ CL)

- **Hepatic impairment**
  - Na and H₂O retention
  - Hepatic congestion (↓ CL)
  - ↓ protein binding (↑ V → ↑ t½)
  - ↓ presystemic metabolism

- **Acute phase response**
  - ↑ α₁ acid glycoprotein (↓ V → ↑ t½)

- **Small bowel disease**
  - ↓ extent of absorption
Chronic dosing

![Graph showing chronic dosing with concentration and elimination half lives on the x and y axes respectively.](image-url)
Accumulation

- Steady state conc > single dose conc
- Occurs when dosing interval < 5 half lives (ie almost always)
- Extent of accumulation determined by dosing interval and elimination half life
- 4 - 5 half lives to reach steady state
- 4 - 5 half lives to reach new steady state if half life changes
Hysteresis loop

![Hysteresis Loop Diagram](image-url)
Pharmacodynamics in elderly patients

Age related changes in sensitivity (1):

- Benzodiazepines ($\uparrow$)
- Warfarin ($\uparrow$)
- $\beta_1$ modulators in cardiac tissue ($\downarrow$)
- $\alpha$ modulators ($\downarrow$)
- Hypotensives ($\uparrow$)
Pharmacodynamics in elderly patients

Age related changes in sensitivity (2):

- Most effects of phenothiazines (↑)
- Calcium channel blocking effect on PR interval (↓)
- GI effects of NSAIDs (↑)
- Central effects of anticholinergics (↑)
Homeostatic mechanisms

- Baroreflex
- Thermoregulation
- Posture
- GI integrity
- Volume/electrolyte homeostasis
Adverse drug reactions

Prevalence (%) vs. Age (years)

- Hurwitz
- Seidl et al
Odds ratios and ulcer complications

Odds ratios

4.8
4.6
4.4
4.2
4

60 - 69
70 - 79
80 +

Age (yr)

Langman et al, 1994
Adverse reactions to nitrazepam

Frequency of ADR (%)

Age (years)

Greenblatt & Allen, 1978
Adverse drug reactions

Excess prevalence in older patients

- Pharmacokinetic changes
  - distribution
  - renal function
  - liver volume
- Changes in sensitivity to drugs
  - impaired functional reserve eg BP homeostasis
  - change in “primary” sensitivity eg β receptor sensitivity
- Higher prevalence of disease
- Concomitant drug consumption
FABF during LBNP

**HYV (n=11)**

- Bas Left arm: 4.0 ± 0.5 ml/min/100g
- Bas Right arm: 3.8 ± 0.5 ml/min/100g
- Bas -20: 3.5 ± 0.5 ml/min/100g

**HEV (n=8)**

- Bas Left arm: 4.2 ± 0.5 ml/min/100g
- Bas Right arm: 3.9 ± 0.5 ml/min/100g
- Bas -20: 3.7 ± 0.5 ml/min/100g

**CI (n=3)**

- Bas Left arm: 4.1 ± 0.5 ml/min/100g
- Bas Right arm: 3.9 ± 0.5 ml/min/100g
- Bas -20: 3.6 ± 0.5 ml/min/100g

**VD (n=5)**

- Bas Left arm: 4.0 ± 0.5 ml/min/100g
- Bas Right arm: 3.8 ± 0.5 ml/min/100g
- Bas -20: 3.5 ± 0.5 ml/min/100g
HT treatment and PP performance

\[ \Delta \text{CFF} \quad \text{(Hz)} \]

\[ \Delta \text{SBP load ( % )} \]
Hypertension

Verbal working memory

Placebo

Active