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Student Objectives for this Chapter

- To understand the basics of a Therapeutic Drug Monitoring service
- To describe and understand how changes in physiology effect the pharmacokinetics of drugs in the very young and the elderly

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Therapeutic Drug Monitoring

We can start this topic by talking about the Clinical Pharmacy service, Therapeutic Drug Monitoring. This involves the measurement and interpretation of plasma/serum/blood concentrations in patients.

Why

Therapeutic drug monitoring (TDM) becomes important when:

a) the drug has a narrow therapeutic-toxic range,

b) there is a large variability in pharmacokinetic parameter values between patients,

c) the therapeutic effect is not readily assessed (e.g. antibiotics) or clinical symptoms are to be avoided (e.g. seizure). Not as useful for blood pressure lowering (can measure B.P. directly) or anticoagulants (again measure clotting time directly),

d) there is a direct relationship between Cp or concentration in other biological sample (e.g. saliva) and pharmacological effect,

e) an appropriate (accurate, short turn around, inexpensive) analytical method is available for the drug,

f) the expected or desired therapeutic effect is not observed (may be absorption or compliance problem),

g) a drug with high first pass effect is involved, or

h) a patients has altered and/or variable renal state and the drug is eliminated mostly as unchanged drug in urine (fe less than 1)

Typical drugs

Table 25.2.1 Therapeutic Concentration Ranges

Drug	Therapeutic Concentration Range
Aminoglycoside (gentamicin, tobramycin)	0.5 < - > 8 mg/L
Digoxin	0.5 < - > 2.0 ug/L
Phenytoin	10 < - > 20 mg/L
Theophylline	10 < - > 20 mg/L

Procedure

Pharmacist and physician develop initial dosing recommendations

Information required

- Patient - Age, weight, sex, height, smoker
- Clinical - Drug requirements, clinical status (renal - serum creatinine; cardiac - cardiac output, liver, etc.)

Calculate initial loading dose or maintenance regimen and make recommendations

Organize sample collection and analysis

Accurate Timing in necessary

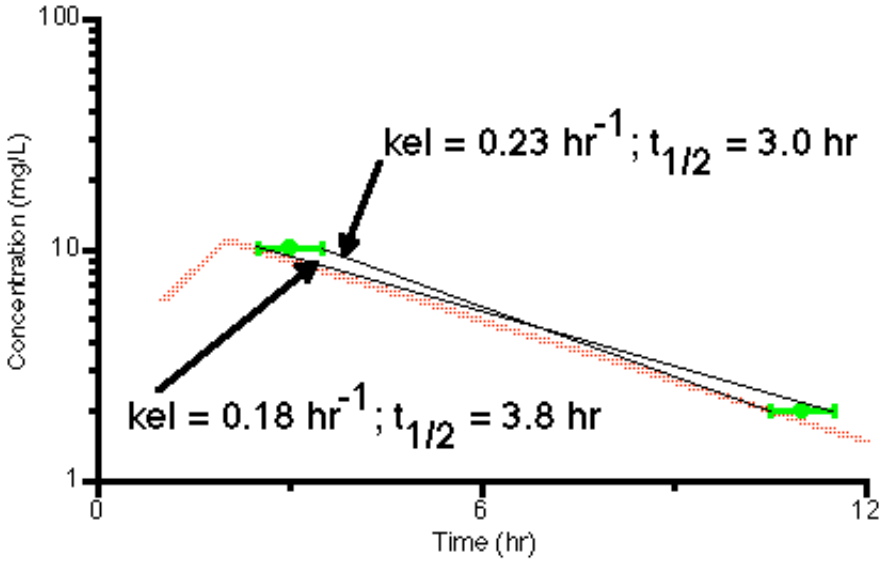

Figure 25.2.1 Illustrating the Effect of Sample Times on Parameter Values

Evaluate pharmacokinetically the analytical result and recalculate dosing regimen recommendations

Organize further samples if necessary, repeat as necessary

Calculations

Computer or calculator programs can be used to help the bedside development of dosing regimen. Other more sophisticated programs are available to calculate values for the drug pharmacokinetics and make further recommendations.

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Pediatric Considerations

The physiologic processes that determine drug disposition undergo radical changes during biological maturation (Morseli 1976, Rane and Wilson 1976, and Shirkey 1973). Thus, the processes of drug absorption, distribution, metabolism, and excretion are modified throughout infancy and childhood. These changes mean that a) drug disposition both changes during maturation and differs from biological norms, and b) a large inter patient variability in drug disposition is observed for many drugs in this patient population.

Further complications are that little data is available concerning the disposition of drugs in infants before the general release of new drugs. Also studies in infants and young children are difficult to perform because of the limited amount of sample which can be collected. The most dramatic changes occur in the first year. For children older than one year, dose adjustments can often be made on a weight or surface area basis without too many problems.

Pharmacokinetic changes

Absorption

Infants after the newborn period have a relative achlorhydria; with gastric acid secretions increasing to reach adult levels at age 3. The bioavailability of acid labile penicillins is increased in newborns.
Delayed gastric emptying and irregular intestinal peristalsis leads to slower absorption of some drugs in infants and young children.

Distribution

Total body water as a fraction of body weight decreases throughout the first year of life (see the Table 25.3.2).

Extravascular fluid is proportionately higher at earlier age as well. In general distribution volumes expressed as volume per body weight tend to be larger in neonates than in adults and decrease towards adult values during childhood. This has been observed for ampicillin, ticarcillin, and amikacin. Binding to plasma proteins appears to be less in newborn infants compared with older children and adults. This appears to be true for both acidic and basic drugs. The presence of competing substances, such as bilirubin in premature infants, complicates the picture.

Metabolism

The various pathways of drug metabolism mature at different rates, and therefore the ability of the newborn to metabolize drugs differs both quantitatively and qualitatively from that of older subjects. No general rules can be developed and a few examples can illustrate the variety of effects observed.

Caffeine is very slowly metabolized in newborns. During the first month almost no metabolism occurs, with half-lives of about 4 days resulting from renal elimination, normally a minor pathway. Between 3 and 7 months, caffeine is metabolized similarly to adults and the half-lives change to adult values during this period. For the similar compound theophylline the half-life was 13 to 29 hours for 8 low birth weight infants.

Glucuronidation is quite inefficient at birth, thus chloramphenicol which is normally glucuronidated in adults and has no major alternate metabolic pathway, the overall elimination is much slower in newborns compared with adults.

Sulfate conjugation is well developed at birth thus newborn paracetamol elimination, predominantly sulfation, is not greatly different from that of adult elimination.

For drugs which undergo M-M or saturable metabolism the effect of age is interesting. For phenytoin, Km is not changed with age, but the maximum metabolism rate, Vm falls progressively with younger patients.

Excretion

Glomerular filtration and renal tubule function in premature infants and newborns is somewhat immature. GFR, normalized for body surface area, increases gradually reaching adult values at about 6 months.

Table 25.3.1 Glomerular Filtration Rate at Various Ages

Age	GFR (ml/min/m2)
First four days	1
14 days	22
One year	70
Adult	70

Renal tubular capacity, measured by renal clearance of *p* -aminohippurate, achieve adult values 1 to 2 months later. Therefore drugs which depend primarily on the renal route of elimination, such as gentamicin, ampicillin, and furosemide, have prolonged elimination times in neonates and young infants.

Table 25.3.2 Physiologic Differences between Neonates and Adults of Pharmacokinetic Importance From Hilligoss 1980

	Neonate	Adult
Gastric acid output (mEq/10kg/hr)	0.15	2
Gastric emptying time (min)	87	65
Total body water (% of body weight)	78	60
Extracellular water (% of b.wt.)	44	19
Intracellular water (% of b.wt.)	34	41
Adipose tissue (% of b.wt.)	12	12-25
Serum albumin (gm/dL)	3.7	4.5
Glomerular filtration rate (ml/min/m2)	11	70

Table 25.3.3 Pharmacokinetic Parameter Values for Infants and Children compared with Adult values From Miles 1983

Age group	**Volume term (L/kg)**	**Half-life (hr)**	**Total body clearance (ml/min/kg)**
Theophylline			
Premature neonates	0.62 (0.19-1.0)	26.9 (14.4-57.7)	19 (6.3-29.9)
Infants	0.44 (0.16-0.83)	4.6 (0.8-8.6)	76 (28-156)
Children	0.44 (0.20-0.68)	3.4 (1.9-8.5)	95 (60-221)
Adults	0.47 (0.33-0.72)	5.7 (2.9-8.3)	65 (32-131)
Gentamicin	Vc		TBC (ml/min/1.73 m2)
Preterm infants and full-term infants	0.48	5.7	21.0
Infants and children	0.28	1.4	130
Adults	0.21	2.1	95
Chloramphenicol	Vd		TBC (ml/hr/kg)
Infants (11-56 d)		10	
Infants (1-12 mo)	0.90	5.5	50-400
Children (1-11 yr)	0.90	4.4	100-400
Adults	0.4-0.9	2-5	100-300

Dosing recommendations

For some drugs detailed pharmacokinetics development of dosage regimens for pediatric patients is not practical. Either there isn't enough good data to make an accurate estimate of dose regimen or there is too much intra- patient variability in parameter values. Alternately, dosage regimens can be determined from various reference texts such the Pediatric Dosage Book. For very young infants and neonates the primary literature should be consulted.

Minimal adjustments can be based on weight, surface body area, or age. Dosing based on weight, e.g. per mg doses or Clark's rule

$$\text{Child Dose} = \frac{\text{weight in lb} \cdot \text{adult dose}}{150}$$

Dosing based on surface area, e.g. per m^2

Dosing based on age, e.g. Young's rule for children older than 2 years

$$\text{Child Dose} = \frac{\text{age (yr)}}{\text{age (yr)} + 12} \cdot \text{adult dose}$$

References

- Morseli, P.L. 1976 Clinical pharmacokinetics in neonates, *Clin. Pharmacokin.*, **1**, 81-98
- Rane, A., and Wilson, J.T. 1976 Clinical pharmacokinetics in infants and children. *Clin. Pharmacokin.*, **1**, 2-24
- Shirkey, H.C. 1973 **Pediatric Dosage Handbook**, Amer. Pharm. Assoc., Washington, DC
- Hilligoss, D.M. 1980 Chapter 5 "Neonatal Pharmacokinetics" in **Applied Pharmacokinetics**, Evans, W.E., Schentag, J.J., and Jusko, W.J. ed., Applied Therapeutics, San Francisco, CA Table 1, p 88
- Miles, M.V. 1983 "Pediatric Pharmacokinetics" in **Applied Clinical Pharmacokinetics**, ed Mungall, D.R., Raven Press, New York, NY, pp 367-388
- Taketomo, C.K., Hodding, J.H. and Kraus, D.M. 2004 Lexi-Comp's Pediatric Dosage Handbook, 11th ed., Lexi-Comp., Hudson, OH

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Geriatric Considerations

Although geriatric patients constitute only 11% of the population in North America, they incur 30% of the total costs of drugs. Within the next 30 years these figures are expected to reach 16-18% and 40%, respectively. Although the elderly are a major group of drug users, most drug studies are performed on patients or volunteers aged 55 years or less. There is a sevenfold increase in drug toxicities as one ages from 20 to 79 years (from 3% at 20-29 years to 21% at 70-79 years). Part of this increase may well be due to multiple medication - drug interactions. I would like to suggest also that a significant part of this increase in drug toxicities is due to incomplete understanding of changes in the ADME processes of drug disposition with aging. We will consider some of the physiological changes which occur in aging and then look at the ADME processes in turn (Garnett and Barr 1984, Triggs and Nation 1975, Vestal 1978, Sjoqvist and Alvan 1983, and Ho and Triggs 1984).

Physiologic changes with age

Easier to look at as a table of factors, Table 25.4.1. Then when considering ADME we can expand on this.

Table 25.4.1 Summary of Factors affecting Drug Disposition and Responses in the Elderly from Massoud 1984a

	Altered Physiology	Clinical Consideration
Absorption	↓ gastric acid secretion, ↑ gastric pH, ↓ GI blood flow, ↓ pancreatic trypsin, ↓ GI motility	Altered dissolution rate, possible decreased absorption rate, time of onset delayed
Distribution		
Body Composition	↓ total body water, ↓ lean body weight, ↑ body fat (female > male)	Polar drugs tend to have ↓ Vd,lipid-soluble drugs ↑ Vd
Protein Binding	↓ serum albumin, ↔ ↑ α^1 GP, ↔ ↑ gamma globulin, ↔ ↓ RBC binding	↑ free fraction of acidic drugs, ↔ ↓ free fraction of basic drugs
Metabolism	↔ ↓ enzyme induction, ↓ hepatic blood flow, ↓ hepatic mass, ↔ acetylation, ↔ ↓ glucuronidation, ↔ ↓ mixed function	decreased metabolism and clearance influenced by environmental factors (e.g.smoking,nutrition) oxidation system
Excretion	↓ GFR, ↓ renal plasma flow, ↓ active secretion	decreased renal clearance, ↑ half-life

Pharmacokinetic changes

Absorption

As noted in the table there are a number of physiologic changes which potentially will alter drug absorption. GI motility, pH changes, etc. There has been little evidence, however, to suggest that this is of major consequence. Reduced absorption in the elderly has been observed for some compounds which are actively absorbed (e.g. galactose, calcium, thiamine, and iron). The absorption of most drugs by passive processes is not generally affected. Only tmax was reduced for tolbutamide in the elderly versus young. For other drugs studied, including l-DOPA, metoprolol, propranolol, cimetidine, and digoxin no changes were observed which could be ascribed to absorption alone. Higher Cpmax values were observed in a number of cases, however, most of these changes could be explained by changes in distribution or clearance.

Distribution

Changes in body composition may occur as the patient ages. Body fat may increase from 15% to 30% and lean body weight may decreases in proportion to total body weight. This should give lower V values for drugs which stay in the central compartment, while lipid soluble drugs would have somewhat larger apparent V values. The apparent volume of distribution for diazepam and chlordiazepoxide in the elderly is larger, whereas, the volumes for lorazepam and oxazepam were relatively unchanged. The lipid solubility of the first two drugs is much higher than for the second pair.

Although total plasma protein concentrations remain relatively constant, albumin concentrations are lower in the aged. The fraction of unbound phenytoin increases 25 to 40% in the aged, however, as earlier described this would also lead to increased clearance. In the case of diazepam it has been found that the percentage unbound could be correlated with age for females, but not males. Drug interactions based on protein binding, and other factors, can be more pronounced in the elderly because they tend to be taking more drugs.

Cardiac output in the elderly is reduced, thus distribution to the kidneys and liver are expected to be reduced. For high extraction drugs this could alter the overall elimination of the drug.

Metabolism

The liver is the major organ involved in metabolism and as shown in the table, liver blood flow and liver mass tend to decrease with

age. Protein binding also is reduced, especially to albumin, as mentioned in the previous section. The third determinant of drug metabolism, intrinsic clearance is quite variable and dependent on the metabolic pathway.

Acetylation appears to be unchanged with age, isoniazid clearance is not altered. It appears that for some drugs which undergo Phase I metabolism (oxidations, reductions) metabolism reduces with increasing age. Examples are lidocaine, phenytoin, propranolol, theophylline. For other drugs which undergo Phase II metabolism (conjugations) the metabolism does not appear to change greatly with age. Some example drugs are isoniazid (acetylation), temazepam (glucuronidation).

Elimination

With increasing age the glomerular filtration process is reduced by a reduction in kidney size (20%), reduction in the number of nephrons (35%), reduction in the number of functioning glomeruli (30%), and a decrease in renal blood flow (40- 50%). Serum creatinine is also decreased with age because of the reduced muscle mass. However, the formulas presented earlier in the section on renal disease can be used to calculate creatinine clearance as a function of age and thus make dosage regimen adjustments. Drug which are renally excreted and for which dosage adjustments should be made in elderly patients include; the aminoglycosides, digoxin, lithium, methotrexate, quinidine, and the tetracyclines (except doxycycline).

An illustration of the type of change in pharmacokinetics with age is shown in the following table.

Table 25.4.2 Pharmacokinetic Data in the Elderly and the Young from Massoud 1984a

	Elderly			Young		
Drug	**Vd (L/kg)**	**$t_{1/2}$ (hr)**	**CL**	**Vd (L/kg)**	**$t_{1/2}$ (hr)**	CL
Ampicillin	0.3 ± 0.04	6.7 ± 5.9	0.08 L/hr/kg	0.3 ± 0.04	1.7 ± 0.5	0.18
Chlordiazepoxide	0.38	40	10 ml/min	0.26	7	30
Digoxin	4.1 ± 0.9	70 ± 13	0.8 ± 0.2 ml/min/kg	5.3 ± 0.6	37 ± 4.5	1.7 ± 0.2
Nitrazepam	4.8 ± 1.7	40 ± 16	4.7 ± 1.5 L/hr	2.4 ± 0.8	29 ± 7.4	4.1 ± 2
Phenylbutazone	0.1 ± 0.02	87 ± 11	2.75 ml/min/kg	0.16	110	2.9
Warfarin	0.2 ± 0.01	44 ± 10	3.3 ± 0.5 ml/min/kg	0.2 ± 0.3	37 ± 2	3.8 ± 0.6

Dosing recommendations

The effects of age on drug disposition depend on the particular compound in question and the characteristics of the population being studied. When evaluating geriatric studies **it is important to distinguish between long-term-care patients who are not considered to be healthy and the active who are older (age > 65 years maybe higher) and living in the community.** Some of the changes ascribed to the elderly may be due to immobility of the patient or an underlying disease or diseases. Also because of changing body composition between males and females it is often important to distinguish between these groups.

In terms of dosage regimen adjustment, for some drugs, such as the aminoglycosides dose adjustment is progressive with a steady change in creatinine clearance with age reflecting the similar change in the clearance of the drugs under question.

References

- Semla, T.P., Beizer, J.L. and Higbee, M.D. 2003 Lexi-Comp's Geriatric Dosage Handbook, 9th ed., Lexi-Comp, Huson, OH ISBN 1-59195-067-8
- Garnett, W.R. and Barr, W.H. 1984 **Geriatric Pharmacokinetics**, The Upjohn Company, Kalamazoo, MI (Publication #8800-86)
- Triggs, E.J. and Nation, R.L. 1975 Pharmacokinetics in the Aged: A Review. *J. Pharmacokin. Biopharm.* , **3**, 387-418
- Vestal, R.E. 1978 Drug Use in the Elderly: A Review of Problems and Special Considerations. *Drugs*, **16**, 358-382
- Sjoqvist, F. and Alvan, G. 1983 Aging and Drug Disposition - Metabolism. *J. Chron. Disease*, **36**, 31-37
- Ho, P.C. and Triggs, E.J. 1984 Drug Therapy in the Elderly. *Austral. NZ J. Med.* , **14**:179-190
- Massoud, N. 1984a Chapter 15 "Pharmacokinetic Considerations in Geriatric Patients" in **Pharmacokinetic Basis for Drug Treatment** ed Benet, L.Z., Massoud, N., and Gambertoglio, J.G., Raven Press, New York, NY, Table 2, page 286.
- Massoud, N. 1984b Chapter 15 "Pharmacokinetic Considerations in Geriatric Patients" in **Pharmacokinetic Basis for Drug Treatment** ed Benet, L.Z., Massoud, N., and Gambertoglio, J.G., Raven Press, New York, NY, Table 3, page 297

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