Clinical Applications of Pharmacokinetics

Objectives

- Understand the basics of a Therapeutic Drug Monitoring Service
- Describe and understand how changes in physiology effect drug pharmacokinetics in the very young and the elderly

Therapeutic Drug Monitoring

- What is it?
- Individualized drug dosing
- Drug concentrations measured in the patient
- Drug concentrations analyzed using pharmacokinetics
- Dose adjustments based on pharmacokinetic parameters determined in patient

TDM Service

- Why?
- Drug has a narrow therapeutic window
  - ratio of MTC to MEC small
- Large variability in pharmacokinetic parameters between patients
  - especially true when there is extensive metabolism
  - high first-pass effect

Why? contd…

- Therapeutic effect is not readily assessed or clinical symptoms to be avoided
  - antibiotics
  - seizure control, heart disease
- There is a direct effect between Cp and drug effect
- There is an appropriate assay available
  - accurate, short turn-around, inexpensive

Why? contd……

- expected or desired effect not observed
  - maybe absorption or compliance problem
- patient has altered or/and variable renal state

Example Drugs

- Aminoglycosides such as gentamicin and tobramycin (0.5 - 8 mg/L)
- Digoxin (0.6 - 2 µg/L)
- Phenytoin (10 -20 mg/L)
- Theophylline (10 - 20 mg/L)
- Cyclosporine (0.15 - 0.4 mg/L)

TDM Procedure

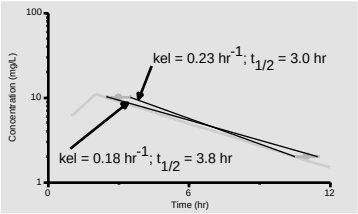
- Pharmacist and Physician develop initial dosing recommendations and target concentrations
- Information required
  - Patient - age, weight, sex, height, smoker,
  - Clinical - clinical status (renal - creatinine clearance, cardiac - CO, liver, etc.)

TDM Procedure contd...

- Calculate initial loading (and maintenance dose) and make recommendation
- Organize sample collection and analysis

TDM Procedure contd...

- Sample Collection
- Accurate timing required



TDM Procedure contd…

- Evaluate result pharmacokinetically
- Recalculate dosing regimen
- Organize further samples are required

Calculations

- Population average parameter values
  - Nomograms - initial dosage regimen calculations
- Parameter determination and dose calculations performed this semester
- Calculator/computer programs to perform pharmacokinetic calculations
  - Abbott program, ADAPT, Boomer, NONMEM, etc.

Assay Methods

- Once established - performed by Pathology or Clinical Chemistry Laboratory
- Early development may be set-up by Pharmacy department
- Required characteristics
  - Speed (turn-around), accuracy, specificity, sensitivity, ruggedness

Assay Methods

- Separation
  - Centrifugation
  - Extraction
  - Chromatography
- Quantitation
  - UV
  - Fluoresence
  - Radioactivity

Assay Methods

- High performance liquid chromatography (HPLC)
- Gas liquid chromatography (GLC)
- Radioimmunoassay (RIA)
- Enzyme multiplied immunoassay (EMIT)
- Fluoroimmunoassay (FIA)

Pediatric Pharmacokinetics

Pediatric Pharmacokinetics

- Physiological changes
- Changes in disposition
- Large interpatient variability as different infants mature differently
- Data sparse
- Most dramatic changes in early days, weeks, months > first year

Pharmacokinetic Changes

- Absorption
  - Relative achlorhydria - less acidic stomach contents - better absorption of acid labile drugs
  - Delayed gastric emptying - slower absorption

Distribution

- Total body water is more as a fraction of body weight in the very young
  - Total body water 78% (neonate) vs 60% in adult
  - Extracellular water 44% vs 19%
  - Volume of distribution larger /kg
- Protein binding reduced
  - Bilirubin in premature infants can displace various compounds

Metabolism

- Various metabolism routes mature at different rates
  - Caffeine is very slowly metabolized in newborns
    - $t_{1/2}$ about 4 days in first month
    - closer to adult after 3-7 months
  - Gluronidation inefficient at birth
    - Chloramphenicol elimination much slower

More Metabolism

- Sulfate conjugation similar from birth
- For phenytoin Km similar but Vm is lower at younger age

Excretion

- Glomerular filtration rate lower
  - First four days > 1 ml/min/m2
  - 14 days > 22 ml/min/m2
  - 1 year and beyond > 70 ml/min/m2
- Reduced elimination of gentamicin, ampicillin, and furosemide in neonates and very young

Examples - Theophylline

	Volume (L/kg)	Half-life (hr)	TBC (ml/min/kg)
Premature	0.62	26.9	19
Infants	0.44	4.6	76
Children	0.44	3.4	95
Adult	0.47	5.7	65

From: Miles, M.V. 1983 "Pediatric Pharmacokinetics" in 'Applied Clinical Pharmacokinetics', ed Mungall, D.R., Raven Press, New York, NY, pp 367-388

Examples - Gentamicin

	Volume (L/kg)	Half-life (hr)	TBC (ml/min per 1.73 m^2)
Premature Full-term Infants	0.48	5.7	21
Infants Children	0.28	1.4	130
Adult	0.21	2.1	95

From: Miles, M.V. 1983 "Pediatric Pharmacokinetics" in 'Applied Clinical Pharmacokinetics', ed Mungall, D.R., Raven Press, New York, NY, pp 367-388

Example - Chloramphenicol

	Vd (L/kg)	Half-life (hr)	TBC (ml/hr/kg)
Infants 11-56 d		10	
Infants 1-12 mo	0.9	5.5	50-400
Children 1-11 yr	0.9	4.4	100-400
Adults	0.4-0.9	2-5	100-300

From: Miles, M.V. 1983 "Pediatric Pharmacokinetics" in 'Applied Clinical Pharmacokinetics', ed Mungall, D.R., Raven Press, New York, NY, pp 367-388

Dosage Recommendations

Pediatric Dosing Book?

- Based on weight

$$\text{Child Dose} = \frac{\text{Wt(lb)} \bullet \text{Adult Dose}}{150}$$

- Based on age

$$\text{Child Dose} = \frac{\text{Age(yr)}}{\text{Age(yr)}+12} \bullet \text{Adult Dose}$$

Geriatric Pharmacokinetics

Geriatric Pharmacokinetics

- 11% of the population - 30% of the prescriptions (old numbers)
  - to approach 16-18% - 40%
- Increased toxicity - multi-pharmacy
- Drug interactions

Physiological Changes

	Altered Physiology	Clinical Consideration
Absorption	Gastric acid Gastric pH GI blood flow Trypsin/motility	Altered dissolution rate, decreased absorption, time of onset delayed
Distribution Body Composition	Total body water Lean body weight ⇔ Body fat	Polar drugs tend to have reduced Vd
Distribution Protein Binding	Serum albumin ⇔ Other protein	Increased free fraction of acidic drugs Less effect on basic drugs

From Massoud, N. 1984 Chapter 15 "Pharmacokinetic Considerations in Geriatric Patients" in 'Pharmacokinetic Basis for Drug Treatment' ed Benet, L.Z., et al., Raven Press, New York, NY, Table 2, page 286

Changes contd

	Altered Physiology	Clinical Consideration
Metabolism	Enzyme induction Hepatic blood flow Liver mass ⇔ Acetylation, glucuronidation	Decrease metabolism and clearance
Excretion	GFR Renal plasma flow Active secretion	Decreased renal clearance Half-life

From Massoud, N. 1984 Chapter 15 "Pharmacokinetic Considerations in Geriatric Patients" in 'Pharmacokinetic Basis for Drug Treatment' ed Benet, L.Z., et al., Raven Press, New York, NY, Table 2, page 286

Absorption

- Minor effects
- Reduced absorption of some actively absorbed drugs
- Tolbutamide - reduced $t_{1/2}$ in elderly

Distribution

- Considerable change in distribution
- Body weight may increase 15 - 30% with a relative reduction in lean body weight
  - Smaller V for polar drugs
  - Larger V for lipid soluble drugs
- Other elderly may have reduced body weight
- Binding reduced at older age
- Reduced cardiac output

Metabolism

- Reduced liver blood flow and mass
  - Reduced metabolism
  - Binding reduced
  - Intrinsic clearance change depends on the pathway
- Biggest reductions with Phase I type metabolism (in general ??)

Excretion

- Reduced GFR due to reduced number of nephrons, number of functioning nephron, and decreased renal blood flow
- Adjustment may be necessary for aminoglycosides, digoxin, lithium, etc.

Examples

- Ampicillin
  - $t_{1/2}$(elderly) 6.7 hr vs $t_{1/2}$(young) 1.7 hr
- Chlordiazepoxide
  - $t_{1/2}$(e) 40 hr vs $t_{1/2}$(y) 7 hr
  - TBC(e) 10 ml/min vs TBC(y) 30 ml/min
- Digoxin
  - $t_{1/2}$(e) 70 hr vs $t_{1/2}$(y) 37 hr
  - TBC(e) 0.8 ml/min/kg vs TBC(y) 1.7 ml/min/kg

From Massoud, N. 1984 Chapter 15 "Pharmacokinetic Considerations in Geriatric Patients" in 'Pharmacokinetic Basis for Drug Treatment' ed Benet, L.Z., et al., Raven Press, New York, NY, Table 2, page 286

Examples

- Nitrazepam
  - Vd(e) 4.8 L/kg vs Vd(y) 2.4 L/kg
  - $t_{1/2}$(e) 40 hr vs $t_{1/2}$(y) 29 hr
- Phenylbutazone
  - Vd(e) 0.1 L/kg vs Vd(y) 0.16 L/kg
- Warfarin
  - changes rather small

From Massoud, N. 1984 Chapter 15 "Pharmacokinetic Considerations in Geriatric Patients" in 'Pharmacokinetic Basis for Drug Treatment' ed Benet, L.Z., et al., Raven Press, New York, NY, Table 2, page 286

Dosing Recommendations

- Distinguish between healthy elderly and patient
- Some changes related to changes in renal function

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