Principles and Practice of Therapeutic Drug Monitoring

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Objectives

• Review pharmacokinetic principles
• Describe the principles of TDM
• Solve common pharmacokinetic problems
Chemistry of Drugs

• Acidic drugs contain a carboxylic group
  – $\text{R-COOH} \leftrightarrow \text{R-COO}^- + \text{H}^+$
  – Strong acids (salicylates, penicillins, analgesics) have pKa’s < 5.0
  – Fully dissociated at blood pH of 7.4
  – Weak acids (barbiturates, acetaminophen, sulfonamides, thiazides) have pKa’s = 5 – 11
  – Weak acids have significant amounts of unionized form present at blood pH.
  – Due to acidic pH of urine, weak acids that are ionized at pH 7.4, may become unionized in urine and prone to greater resorption
Chemistry of Drugs

• Basic Drugs contain an amine group
  – \( R\text{-NH}_3^+ \leftrightarrow R\text{-NH}_2 + H^+ \)
  – Basic drugs can act as weak bases (anesthetics, opiates, antidepressants with pKa’s < 10 or strong bases (amphetamines and bronchodilators)
  – Bases tend to be significantly ionized at blood pH

• Neutral drugs do not carry a charge.
  – They can be lipophilic (corticosteroids) or polar (digoxin)
Pharmacokinetics

• LADME model
  – Liberation – release of drug from formulation
  – Absorption – speed and fraction of dose that enters circulation
  – Distribution – ability of drug to move throughout the body to tissue cells
  – Metabolism – chemical conversion of active drug to inactive metabolites
  – Excretion – elimination of drug from body
Liberation

• Formulation can affect the rate and extent of absorption (solutions, suspensions, immediate release tablets, sustained-release pills, enteric coated tablets)

• Chemical nature of drug can affect rate and extent of absorption.
  – Free acids/bases are unionized – pass membranes faster than ionized salts
  – Weight equivalents differ – salts account for counterion in weight of formulation
  – Some drugs have precursors to active drugs (primidone metabolized to phenobarbital or amitriptyline to nortriptyline)
  – Precursors may have biologic activity distinct from active metabolites
Absorption

- Rate of absorption affects peak conc
- Extent of absorption affects both peak conc and total AUC vs time curve
- Gastric emptying rate, gastric pH, GI blood flow, intestinal absorption sites and coadministration of food can affect both rate and extent of absorption
- Bioavailability (f) – amount of dose available to act at body receptors
  - Loss can occur during absorption or through liver metabolism
  - F = (% absorbed) x (% escaping first-pass metabolism)
Plot of $C_p$ versus Time for A and B with B having Slower Absorption
Distribution

• After absorption, drugs distribute throughout the body via circulatory, lymphatic and tissue fluids.
• Amount of free drug available to act at organ receptors is affected by both protein and tissue binding
• Acid-neutral drugs bind albumin
• Basic-neutral drugs bind α-1-acid glycoprotein
• Free drug affected by disease alterations in these proteins (liver disease and albumin or acid glycoprotein an acute phase/stress reactant)
Volume of Distribution

Drug concentration in beaker:
- Dose = 10 mg
- \( C_p^0 = 20 \text{ mg/L} \)
- Apparent Volume = 500 ml

With charcoal in beaker:
- Dose = 10 mg
- \( C_p^0 = 2 \text{ mg/L} \)
- Apparent Volume = 5000 ml
Volume of Distribution

• Vd is pharmacokinetic parameter relating serum/plasma concentration to total amount of drug in body.
• Total volume of body water (0.6 L/Kg)
• Apparent Vd greater than body water indicates tissue and protein binding
  – Vd = (amount of Drug in body)/(Serum conc)
  – Vd = Dose/C
Audience Poll

- A 70 Kg man takes a 5 mg phenobarbital dose (Vd = 1 L/Kg). What is the maximum plasma phenobarbital concentration you can expect?
  A. 7 μg/L
  B. 70 μg/L
  C. 700 μg/L
  D. 5 μg/L

- Hint: Dose / Vd = C
Volume of Distribution Example

\[
\text{Dose} = \text{Conc} \\
Wt \times Vd
\]

\[
5 \text{ mg} = 0.07 \text{ mg} = 70 \mu g/L \\
70 \text{ Kg} \times 1\text{L/Kg} = \text{L}
\]
Audience Poll

• What is the loading dose required for drug A (V_d is 0.75 L/kg) if only 70% is bioavailable and target concentration is 10 mg/L in a 75 Kg patient?
  A. 400 mg
  B. 550 mg
  C. 700 mg
  D. 800 mg

- Hint: f (Dose) = C * Vd
Answer

- Dose = Target Concentration x Vd
- \( V_d = 0.75 \text{ L/kg} \times 75 \text{ kg} = 56.25 \text{ L} \)
- Target Conc. = 10 mg/L
- Dose = 10 mg/L \times 56.25 \text{ L}
- = 565 mg
- Dose is only 70% available, so
  \( 565 / 0.7 = 807 \text{ mg total} \)
- This would probably be rounded to 800 mg
Metabolism

- Metabolism alters the chemical structure of the drug. Lipophilic molecules become more polar to enhance elimination.
- Metabolism can be spontaneous or enzyme mediated.
- Only free, unbound fraction is available for tissue receptor binding and enzymatic metabolism.
  - Active (procainamide – N-acetyl procainamide)
  - Inactive (theophylline – 3-methylxanthine)
  - Partially active (lidocaine – monoethylglycinexylidide)
Metabolism

• Enzyme metabolism demonstrates saturation kinetics at high drug conc

• Michaelis-Menten equation
  – Metabolism Rate = \( v = \frac{V_{\text{max}} \times C}{K_m \times C} \)
  – \( K_m = \) Michaelis constant = rate at half max
    \[ = \frac{V_{\text{max}}}{2} \]
  – First order low drug conc \( C \ll K_m \) – Linear
    • \( V = \frac{V_{\text{max}}}{K_m} \times C \)
      \( V_{\text{max}}/K_m \) is a constant
  – Zero order high drug conc \( C \gg K_m \) – saturated and independent of concentration
    • \( V = \frac{V_{\text{max}} \times C}{C} = V_{\text{max}} \)
Michaelis Menten Kinetics

Michaelis–Menten plot relating the reaction rate $v$ to the substrate concentration $[S]$. 

$V_{\text{max}}$ 

$\frac{V_{\text{max}}}{2}$ 

$K_M$ 

$[S]$
Audience Poll

• Legal limits of intoxication are 1 mg/mL in plasma. If ethanol has a constant, zero order elimination rate of 10 mL/hr, at what rate must ethanol be consumed to maintain a level of intoxication?
  A. 1 mL/hr
  B. 10 mL/hr
  C. 100 mL/hr
  D. 1000 mL/hr
Answer

• To maintain steady-state concentration, the rate of absorption must equal the rate of elimination.

  10 mL/hr elimination = 10 mL/hr absorption
Elimination

• Sum of all clearance pathways:
  – $Cl_{\text{total}} = Cl_{\text{renal}} + Cl_{\text{hepatic}} + Cl_{\text{pulmonary}} + ...$
  – Hepatic clearance depends on drug delivery to liver (blood flow $Q$) and metabolic enzyme activity (extraction ratio $(E)$)
    • $Cl_{\text{hepatic}} = Q \times E$
  – Renal clearance depends on free filtration through glomerulus and rate of reabsorption
    • $Cl_{\text{renal}} = (\text{Filtration} + \text{Secretion}) \times (1 - \text{reabsorption})$
    • Filtration Clearance = GFR $\times$ $Fu$  [$Fu = \text{unbound fraction drug}$]
    • Normal GFR = 100 – 125 mL/min
    • >125 mL/min means secretion while
    • < 100 mL/min means reabsorption or renal impairment
  – Rate of elimination $(K)$
    • $K = C \times (Cl_{\text{total}})$ or $K = (Cl_{\text{total}}) / (Vd)$
Audience Poll

• What maintenance dose is required for drug B if the target average SS concentration is 10 mg/L and CL of drug B is 0.015 L/kg/hr in a 75 Kg patient?
  A. 240 mg
  B. 270 mg
  C. 330 mg
  D. 400 mg

• Hint: Loading Dose = K = CL * C_{SS}
Answer

- Maintenance Dose = CL x CpSS_{av}
- CL = 0.015 L/hr/kg x 75 = 1.125 L/hr
- Dose = 1.125 L/hr x 10 mg/L
  = 11.25 mg/hr
- So will need 11.25 x 24 mg per day
  = 270 mg
Half-Life

• Repeated dosing of drugs builds higher concentrations of drug upon drug concentration remaining from previous dose.
• Repeat dosing at the drugs half-life builds to a steady state concentration in 5 doses.
• Achievement of steady-state drug levels is based on intermittent dosing schemes when drug dosed at half-life
  • \( T_{1/2} = 0.693 / K = 0.693 \times \left[ \frac{Vd}{Cl} \right] \)
  • \( C_{ss} = \frac{K}{Cl} = 0.693 \times \left[ \frac{Cl \times t_{1/2}}{f \times D} \right] / Vd \)
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Therapeutic Response

• Pharmacologic response of patient to a given dosage regimen determined by:
  – Patient compliance
  – Dose
  – Rate of administration
  – Rate of drug elimination
  – Access of drug to cell receptor sites
  – Receptor sensitivity

• Therapeutic index – ratio of the dose required to damage cells compared to the dose necessary for therapeutic effect
Drug Peaks versus Area Under the Curve

- Peak concentration – maximum level of drug attained in body fluid
- Area Under the Curve – total concentration of drug over time available to bind to cells for therapeutic effect
Plasma Concentration (mg/L)

Peak Concentration

Peak

Area under the Curve (AUC)

Time of Peak

Time (hr)
Drug Concentration Homogeneity

- Therapeutic monitoring assumes equilibrium between serum drug concentration and tissue concentration.
- During absorption and distribution, drug concentrations higher in serum than at tissue cell surface, because drug hasn’t had time to distribute.
\[
\text{Semi-log}
\]

Intercept = \( A = \frac{F \cdot \text{DOSE} \cdot \text{ka}}{V \cdot (\text{ka} - \text{kel})} \)

Cp\text{late}

Straight line portion described by one exponential

slope (ln) = -\text{kel}
The Therapeutic Range

• Range of drug concentrations where most patients receive maximum benefit from the drug with the fewest side effects.
• Too high – patients experience more side effects and risk of toxicity/overdose
• Too low – drug will also not be effective (subtherapeutic)
• Most therapeutic ranges are standardized for collection – easiest to reproduce is trough – blood samples collected just before next dose.
Take Home Message

• Therapeutic Drug Monitoring based on pharmacokinetic equations that rely on accurate timing of blood collections
• Timing and target ranges will vary based on the drug, dosing interval, infection and clinician’s assessment of the patient.
• Gentamicin for example peak concentrations should be collected 30 - 60 minutes after a 30 minute infusion (allows time for drug distribution) – requires proper documentation of administration vs collection timing
Rationale for TDM

- Small therapeutic index – narrow window between therapeutic and toxic conc
- Apparent therapeutic failure – patient who doesn’t respond to standard regimens
- Monitor compliance – verify therapeutic failure is not consequence of not taking drug
- Suspected toxicity – verify drug conc
- Assess levels in unstable settings (drug or disease interactions)
- Individualize therapy and calculate pharmacokinetics – optimize dosage regimen
Summary

• Pharmacokinetics describes how drugs are handled by the body; absorption, distribution, metabolism and clearance.
• Therapeutic drug monitoring allows physicians to monitor and adjust the dosage of drugs with narrow therapeutic indices.
• Don’t get lost in the equations, the math should naturally follow the principles. Understand how drugs distribute and are cleared, and the equations will come naturally.
Review Questions

• **Ethanol distributes in total body water (approx 40 L), if the legal limit for intoxication is 1 mg/mL in plasma, how much pure ethanol must be consumed to reach intoxication levels?**
  
  A – 400 mg  
  B – 40 g  
  C – 4 g  
  D – 40 mL

• **Warfarin (anticoagulant) is about 98% protein bound. For a 5 mg dose, only 0.1 mg of warfarin is free. If a patient takes a normal dose of aspirin at the same time as warfarin (occupies 50% of binding sites), what is the new level of free warfarin in the body?**
  
  A – 0.1 mg  
  B – 0.2 mg  
  C – 0.4 mg  
  D – 2.5 mg

• **A 55 kg woman has a plasma theophylline (Vd = 0.5 L/Kg) concentration of 15 μg/L. How much theophylline does she have in her body?**
  
  A – 200 μg  
  B – 300 μg  
  C – 400 μg  
  D – 500 μg

Answers: 1) B, 2) B, 3) C
Review Questions

• A patient has a potentially toxic digoxin level of 4.5 μg/L. Given that the half-life of digoxin in this patient is 60 hr, and assuming that renal function is stable, how long should the drug be stopped to allow the level to fall to 1.5 μg/L?
  A – 1 day
  B – 2 days
  C – 3 days
  D – 4 days

• A doctor orders 200 mg of Rocephin to be taken by a 7 Kg infant every 8 hrs. The medication label shows that 75 – 150 mg/Kg per day is the appropriate dosage range. What is the most appropriate answer?
  A – The dose is lower than the minimum desired dosage
  B – The dose is within the appropriate dosage range
  C – The dose is higher than the minimum desired dosage
  D – The range cannot be calculated from the supplied information

• Phenobarbital 180 mg/m2/24 hrs is ordered to be given every 8 hours for a child whose BSA (body surface area is 0.29 m2. If this formulation of phenobarbital is only 50% bioavailable, how much should be given at each dose?
  A – 15 mg
  B – 17 mg
  C – 35 mg
  D – 50 mg

Answers: 1) D, 2) B, 3) C