

**Medical Pharmacology Fall Semester 2008**  
**Exam 1 Knowledge Objectives**

**Principles of Drug Disposition and Pharmacokinetics**

(Lectures 1-8)

1) Routes of Administration

Know major enteral and parenteral routes of administration, advantages and disadvantages

Understand first pass effect, and which routes it applies to

Understand difference between iv bolus and iv infusion administration

2) Absorption; Understand passive and active movement of drug molecules across membranes

Organ and tissue-specific factors: types of cell junctions, degree of perfusion

Factors that affect passive diffusion: concentration, water solubility, molecular size,  $K_p$

Understand effects of protonation of weak acids and weak bases on molecular charge (+, -, or neutral)

Understand the importance of the relative values of  $pK_a$  and local pH on protonation (Henderson Hasselbach equation) Remember the graph of % protonation vs. pH that has the same shape for all weak acids and bases

Understand principles of ion trapping, and how this determines net movement from one compartment to another

Bioavailability: Know what F stands for (exactly) What physiological factors determine F?

3) Distribution:

What are the approximate sizes of each fluid compartment?

What is the "physical definition" of the volume of distribution?

What is the mathematical definition of the volume of distribution? Why is this more useful than the physical definition?

How can a volume of distribution be 5x the body size?

What can the volume of distribution be used to calculate?

Know how the following affect drug distribution: blood flow (example of thiopental vs. phenobarbital),  $K_p$ , size

Plasma protein binding: What happens to a drug and its pharmacological activity when it is bound. How does binding of one drug affect binding and pharmacological activity of another? What is the meaning of "% plasma protein bound"?

Know the various types of barriers to drug distribution (capillary, blood/brain, blood /csf, placental)

#### 4) Drug Metabolism:

Know the definition of Phase 1 and Phase 2 reactions. What is the net effect on pharmacological activity and rate of elimination?

Have a general idea of what cytochrome P450 is and how it works. How can a limited number of enzymes metabolize so many molecular species?

Understand the concepts of CYP Inhibition and CYP Induction. What is the practical implication of each?

Recognize the following patterns of CYP-dependent Phase 1 metabolism: Hydroxylation, Dealkylation (and Deamination), Epoxidation, Reduction; and non-CYP-dependent metabolism: dehydrogenation, hydrolysis, reduction

Recognize the following conjugation reactions: Glucuronidation, sulfation, acetylation, amino acid conjugation, glutathione conjugation (mercapturic acid formation)

#### 5) Drug elimination.

What happens to drug molecules in the kidney (filtration, reabsorption, secretion)  
Understand the concept of clearance ratio as it relates to GFR

What molecular factors determine clearance ratio (size,  $K_p$ , charge, affinity for secretion pumps)

Understand the definition of clearance and why it is more useful to define clearance (a constant) than rate of elimination (not a constant)

How are clearance and rate of elimination related?

How does changing urine pH affect drug elimination (ion trapping in the tubular fluid)?

Know what the enterohepatic cycle of drug elimination is

#### 6) Pharmacokinetics

Know what is meant by zero-order elimination, what is constant, and the physiological reason why it occurs (ethanol is the example used)

Know what is meant by first order elimination, what is constant, and how it relates to clearance.

Know what the general shapes of zero- and first -order elimination curves look like.

Know what the first order elimination rate constant is, and how it relates to clearance.

Know the conceptual meaning of half life and how to calculate it from a graph of first order elimination.

Know how  $K_e$  and half life are related.

Understand why 95% of drug is eliminated in 4.5 half lives (regardless of the length of the half life)

Know the following equations:  $V_d = \text{Body burden} / C_p$ ;  $V_d = \text{Dose} / C_0$ ;  $T_{1/2} = 0.693 / K_e$ ;  $K_e = 0.693 / T_{1/2}$ ;  $Cl = V_d * K_e$ ;  $C_{ss} = Q / Cl$  ( $C_{ss} = Q / V_d * K_e$ )

Be able to do the mathematical manipulations on page 19 of the handout

Understand how infusion and clearance balance each other out to produce a steady state concentration for an infused drug. Know how to calculate infusion rate for a given  $C_{ss}$  and vice versa (see above equations)

Know that drug accumulation mirrors drug elimination, and that it takes 4.5 half lives to reach a new steady state. What does the rate at which the  $C_{ss}$  reaches steady state depend on? ( $K_e$ , not  $Q$ ). Understand why a drug with a large  $K_e$  (short half life) reaches steady state faster than a drug with a small  $K_e$  (long half life).

Why is a "loading dose" given? How do you calculate a loading dose. Why is  $C_{ss}$  dependent on the infusion rate, but independent of the loading dose? How would you adjust the loading dose and infusion rate in cases of impaired clearance?

### **Lecture 9: Pharmacogenetics:**

What does this term mean?

What 2 processes are subject to pharmacogenetic variability? (Receptors - minor factor; Drug metabolism - major factor)

Know some historic examples of pharmacogenetic differences: succinylcholine apnea, primaquine toxicity, isoniazid toxicity.

More recent clinically important examples; Thiopurine N Methyl transferase, CYP2D6 (debrisoquine 6-hydroxylase)

Understand (in general terms) some of the genetic variations that produce slow and extensive metabolizer phenotypes

Know the clinical implications of slow, normal and extensive metabolism for drugs that are metabolized by CYP2D6