

Review Document for 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, Kp

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

Understand the importance of the relative values of pKa 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), Kp, 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?

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

ANTI-THROMBOTIC DRUGS

Hemostasis and thrombosis involve: Blood coagulation
 Platelet aggregation

The basis of therapy of thrombosis: Anticoagulants
 Anti-platelet drugs
 Plasminogen activators

Anticoagulants and anti-platelet drugs - to prevent the formation of thrombi
Plasminogen activators - to lyse existing thrombi

Anticoagulants:

Heparin

Mechanism of action: Negatively charged and binds to lysine residues of anti-thrombin 111, thereby activating anti-thrombin III to neutralize thrombin and other clotting factors

Absorption: Highly charged
 Crosses membrane poorly, drug of choice for pregnant women
 Administered parenterally

Complications: Hemorrhage
 Thrombocytopenia

Coumarins - Warfarin (Oral anticoagulants)

Mechanism of action: Vitamin K₁, is required for the conversion of Glu to Gla residues in several clotting factors. Warfarin blocks the reduction of vitamin K₃ to vitamin K₁,.

Absorption: Given orally
 In plasma, 99% is albumin-bound. Only the free form is active.
 Crosses the placenta, cannot be used during pregnancy

Complications: Hemorrhage

Anti-platelet drugs:

Aspirin

Mechanism of action: During platelet activation, arachidonic acid is released and is metabolized by cyclooxygenase to prostaglandin H₂ and thromboxane A₂. The latter two compounds are potent platelet agonists. Aspirin acetylates cyclooxygenase, rendering it inactive.

Complications: Gastrointestinal bleeding
Aspirin also acts on cyclooxygenase on endothelial cells to
block the formation of prostaglandin², a natural platelet
inhibitor - used low doses of aspirin.

Dipyridamole

Mechanism of action: The increase of intracellular calcium in platelets is
essential for platelet activation. Cyclic AMP (CAMP)
sequesters calcium into its platelet storage sites.
Dipyridamole inhibits CAMP phosphodiesterases to
prevent the breakdown of intracellular CAMP, thus
blocking platelet activation.

Complications: Non-specific and not effective

Recommended uses: Used in combination with warfarin to prevent
thromboembolism in patients with artificial heart valves.

Plasminogen Activators:

Fibrinolysis: plasminogen is converted to plasmin which degrades polymerized fibrin in
blood clots.

Drugs used for fibrinolysis:

Tissue-type plasminogen activator (t-PA) - serine protease
 - synthesized by endothelial cells
 - fibrin specific

Urokinase (single chain urokinase-type plasminogen activator) - zymogen
 - synthesized by kidney
 cells
 - fibrin specific

Streptokinase - produced by β -hemolytic streptococci
 - forms a complex with plasminogen and change its conformation
 - NOT fibrin specific, leading to degradation of fibrinogen and fibrin

ANTI-ATHEROSCLEROTIC DRUGS

- Atherosclerosis
- LDL in blood penetrates into the subendothelium and becomes oxidized. Oxidized LDL causes transendothelial migration of monocytes/macrophages which in turn ingest oxidized LDL to form foam cells in fatty streaks. Further proliferation of smooth muscle cells and deposition of extracellular matrix results in atherosclerotic plaque formation.
 - affects large and medium sized arteries
 - elevated LDL and TG levels are associated with increased risk
 - HDL levels are inversely related to risk

Regulation of cholesterol and triglyceride (TG) metabolism:

1. Exogenous pathway: Chylomicrons (CM) are degraded by lipoprotein lipase
Uptake of TG by adipose tissue and muscle
Transport of CM remnants to liver
2. Endogenous pathway: Liver synthesizes and secretes VLDL
VLDL is degraded by lipoprotein lipase to form IDL and LDL
Uptake of IDL and LDL by LDL receptor-mediated endocytosis
3. Reverse transport of cholesterol: As cells die, cholesterol is released and trapped in HDL. Cholesterol in HDL is esterified by LCAT and transferred to VLDL, which then is metabolized to IDL and LDL.
4. De Novo Cholesterol Synthesis: Liver is the major site of cholesterol synthesis
HMG-CoA reductase is the rate limiting enzyme
5. Enterohepatic Circulation: Bile salt is synthesized by the liver, released into the intestine and recycled

- Therapeutic strategy
- identify patients at risks
 - modify diet and lifestyle
 - pharmacologic therapy

Drug Therapy

Bile salt sequestrants

- anion exchange resins binding negatively charged bile acids
- increased cholesterol conversion to bile acid
- increased cholesterol synthesis and LDL receptors in liver
- increased LDL uptake and decreased serum LDL and cholesterol levels
- increased HDL/LDL ratio

Niacin (nicotinic acid)

- inhibits a hormone-sensitive lipase involved in lipolysis in adipose tissue
- decreased free fatty acid available to the liver for TG synthesis

- decreased production and release of VLDL by the liver
- decreased serum levels of VLDL, LDL and TG
- decreased HDL clearance
- increased HDL/LDL ratio

Statins

- HMG-CoA reductase inhibitors
- cells express more LDL receptors
- decreased cholesterol and VLDL production and release by the liver
- decreased HDL clearance - increased HDL/LDL ratio

Fibrates

- stimulate lipoprotein lipase
- increased VLDL clearance
- reduced serum levels of TG and LDL
- decreased HDL clearance
- increased HDL/LDL ratio

Ezetimibe

- Interferes with dietary cholesterol absorption