Drug Excretion

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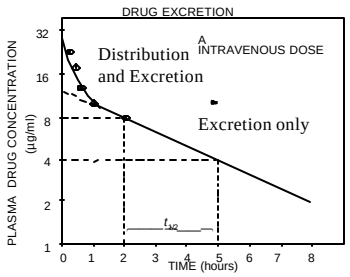
Drug Excretion and Clearance

Drug Excretion: is the movement of drug from tissues and blood to the external environment.

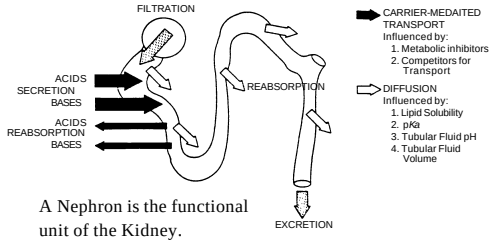
Drug Clearance (CL): is the apparent volume (ml, L) of blood that is cleared of the drug per time period (min, h).

Drug Clearance and Half-Life



Half-life (t ½) is time required to clear 50% of drug.

Renal Drug Clearance



A Nephron is the functional unit of the Kidney.

Glomerular Filtration I

Kidney blood flow is about 650 ml/min.

Glomerulus filters about 20% (130 ml/min). [GFR]

GFR is a good measure of Kidney function.

180 L filtered/day but 99% reabsorbed (urine = 2 L)

Most non-protein drugs are filtered.

Glomerular Filtration II

Non Saturable process.

Drug Clearance is often proportional to GFR.

GFR is reduced in : newborn, elderly, kidney and heart disease.

Reduced GFR: lower drug dose, increase dose interval or both.

Tubular Reabsorption [Passive]

Drug moves from nephron lumen to blood.

Drugs cross membrane by passive diffusion (Fick's Law).

99% of water reabsorbed increases drug level in lumen.

Change urine pH to increase drug ionization and excretion .

$NaHCO_3$ increases pH and ionization of acids: aspirin, PB.

NH_4Cl lowers pH and increases ionization of bases: codeine, amphetamine, meperidine (not used clinically).

Tubular Reabsorption [Active]

Movement of agent from urine to blood.

99% of agent reabsorbed by active transport: sodium, glucose, amino acids, uric acid.

Problem: High plasma uric acid level in gout.

Treatment: Block reabsorption of uric acid with: probenecid or aspirin since these agents saturate uric acid carriers.

Tubular Secretion I

Drugs secreted from blood to lumen of nephron.

Two separate carrier-mediated systems for bases and acids.

Bases: acetylcholine, histamine, atropine, meperidine , etc.

Acids: salicylate, penicillin, probenecid, cephalosporins , etc.

Tubular Secretion II

Competition for carriers within groups [acids with acids, etc]

Penicillin secretion is readily blocked with Probenecid.

Saturation of carriers at high drug doses.

Protein-bound drugs in plasma are readily secreted.

Renal Drug Clearance I

Renal Clearance (volume of plasma cleared of drug/min or hr)

Clearance [CL] = U•V/P

U = urine drug concentration (mg/ml)

P = plasma drug concentration (unbound) (mg/ml)

V = rate of urine flow (ml/min)

Renal Drug Clearance II

The GFR of a normal kidney is 130 ml/min.

If the renal CL of a drug is greater than the GFR:

The drug is primarily secreted (net effect).

PAH [para-aminohippuric acid] is secreted by kidney.

U V P

CL = [65 mg/ml] [1 ml/min] / [0.1 mg/ml] = 650 ml/min [RPF]

Renal Drug Clearance III

If Renal drug clearance is less than GFR then drug is:

Primarily reabsorbed by the Kidney (net effect).

$$CL = \frac{[U]\,[V]}{[P]} = \frac{[50\ mg/ml]\,[1\ ml/min]}{[1\ mg/ml]} = 50\ ml/min$$

Renal Drug Clearance IV

If renal drug clearance is equal to the GFR then:

Drug may not be secreted or reabsorbed [only filtered].

Inulin and creatinine are only filtered by kidney.

$$CL = \frac{[U]\,[V]}{[P]} = \frac{[130\ ml/min]\,[1\ ml/min]}{1\ mg/ml} = 130\ ml/min$$

Factors Altering Renal Drug Clearance

Renal drug clearance is lower [reduce dose] in:

Elderly and Newborn

Women (20%) than men

Kidney and Heart Disease

Patients taking secretion blockers (aspirin, probenecid)

Alternative Drug Clearance Techniques

Extracorporeal Dialysis (Artificial Kidney)

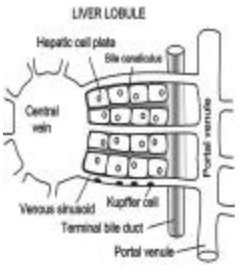
Kidney Failure

Drug Overdose

Hemoperfusion (drug adsorbent)

Drug Overdose

Structure of Liver Lobule



Functional unit of liver

PV brings drugs to liver from GI.

Cell plate is bilayer of liver cells.

CV is surrounded by cell plate.

BC secretes various agents.

TBD connects lobule with gall Bladder.

Hepatic Drug Clearance I

High Extraction Ratio Drugs:

Propranolol, Lidocaine and Morphine

Readily cleared in first-pass through the liver (first-pass effect)

Clearance regulated by blood flow not metabolism

Clearance lower in elderly (lower metabolism and blood flow).

Hepatic Drug Clearance II

Low Extraction Ratio Drugs:

Tolbutamide, Warfarin, Phenobarbital

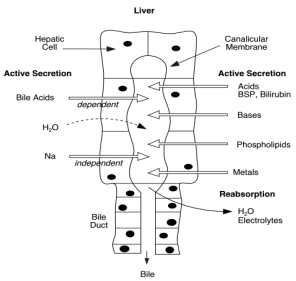
Not readily cleared in their first-pass through the liver.

Clearance regulated by metabolism rather than blood flow.

Clearance lower in newborn and elderly (lower metabolism).

Biliary Drug Excretion I

Cell Plate



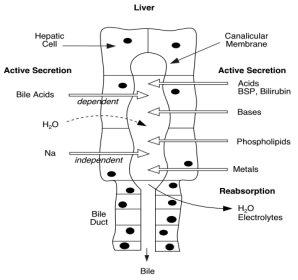
Cell plate is key unit.

Transport proteins enhance drug clearance and excretion.

Secretion of various agents: Na, Bile Acids, PL and Cholesterol produces bile.

Biliary Drug Excretion II

Cell Plate



Drug metabolism key factor.

Secretion of Acids, Bases

Secretion of Estrogens, PL

Secretion of metals (GSH)

Competition for and Saturation of carriers

Assessment of Liver Function

Liver dysfunction results in :

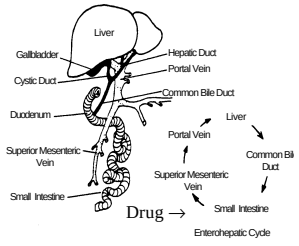
Cholestasis (decreased bile flow)

Reduced Drug Metabolism and Drug Clearance.

Reduced clearance of bilirubin (yellow skin color).**

Reduced clearance of bile acids (increased BA in blood).**

Enterohepatic Circulation of Drugs



Drug Absorption

Drug uptake and metabolism

Drug secretion and hydrolysis

Drug reabsorption

Prolonged duration of action.

Inhibit cycling (cholestryamine)

Agent toxicity (indomethacin)

Gastrointestinal Excretion of Drugs

Orally administered drugs that are not absorbed:
Cholestyramine

Stomach (pH 1-3) traps bases (codeine)

Intestine (pH 6-8) traps acids (aspirin)

Pulmonary Drug Excretion

[Drug in Lung Blood] / [Drug in Lung Air] = λ

Low λ drugs such as Nitrous Oxide (λ = 0.5)

Short duration of action and rapid elimination.

High λ drugs such as methoxyflurne (λ = 12)

Long duration of action and slow elimination.

Elimination rate inversely proportional to λ

Minor Routes of Drug Excretion

Drugs are primarily excreted by passive diffusion.

Salivary Gland drug excretion may produce toxicity to oral mucosa and teeth.

Mammary Gland drug excretion will contaminate milk [mother and cows] consumed by individuals.

Sweat Glands major route of drug elimination in person who profusely sweats (professional athlete or outside worker in hot and humid conditions).