Drug Excretion

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Drug Excretion and Clearance

Drug excretion is the movement of drugs from blood or tissues to the external environment through various media produced by the body:

- fluids (urine, bile, sweat, tears, milk, etc).
- in solids (feces, hair)
- in expired air (volatile compounds only)

Since some drugs can be directly excreted, this is the second major mechanism by which the actions of drugs are terminated.

Drug Clearance (CL) is the apparent volume of plasma that is cleared of active drug per unit time (units are typically mL/min or L/hr).

Illustration of clearance concept

Volume of cube equals volume of plasma that flowed through system in one min.
Amount of drug in Volume is 5000 µg.
In one min., 1000 µg is eliminated, decreasing conc. to 40 µg/mL

Hypothetical volume eliminated in the one min. was 20 mL...
∴ CL = 20 mL/min

Three mechanisms of renal drug clearance

1. Glomerular filtration
   - Renal plasma flow = 650 mL/min
   - 20% undergoes filtration through the glomerular capillaries.

   Normal GFR is ~130 mL/min
   \(0.13L/min \times 60 \text{ min/hr} \times 24 \text{ hr/day} = \sim 180 \text{ L/day}\)

   Measurement of GFR – (inulin or creatinine clearance) (kidney function test).

   Glomerular filtrate
   - Plasma water, sodium, chloride, bicarbonate, urea, glucose, hydrogen ion, potassium ion
   - Drugs or drug metabolites (non protein bound).

   Plasma proteins and protein-bound drugs are too large to be filtered (efficiency of glomerular filtration for any given drug depends on extent of protein binding).

2. Tubular Secretion and Reabsorption
   - Transport of drugs by active processes in the proximal and distal tubules.

   Carriers for transport:
   1. Membrane transport
   2. Competitive transport

   Efflux of drugs:
   1. Lipid Solubility
   2. pH
   3. Tubular Fluid pH
   4. Tubular Fluid Volume

3. Passive Diffusion
   - Movement of drugs down their concentration gradient.

   Factors influencing passive diffusion:
   1. Membrane permeability
   2. Lipid solubility
   3. pH
   4. Tubular Fluid pH
   5. Tubular Fluid Volume

Drug Clearance: definition

Drug Clearance (CL) is the apparent volume of plasma that is cleared of active drug per unit time (units are typically mL/min or L/hr).
Glomerular Filtration II

Filtration is a non saturable process; the amount of drug appearing in the filtrate is proportional to the concentration in plasma.

Drug clearance by the kidneys usually proportional to GFR.

GFR is reduced in: newborns, the elderly, patients with kidney and heart disease.

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

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Tubular reabsorption

Sodium, glucose, amino acids, uric acid, etc. in the GF are reabsorbed by tubular epithelium (carrier-mediated active transport).

Water is reabsorbed passively.

Drugs or drug metabolites can also be reabsorbed (passive diffusion).

Passive reabsorption governed by Fick’s law.

Lipid partition coefficient K

Ionization (pKa and tubular fluid pH)

Concentration gradient increased as water is reabsorbed from filtrate

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Tubular reabsorption of drugs that are weak acids and weak bases

Reabsorption of weak acids or bases can be markedly affected depending on pKa and pH of urine (normal range 4.5 to 8).

Urine pH can be changed to increase drug ionization and drug excretion in drug-intoxicated patients

Phenobarbital (weak acid) overdose: excretion increased by alkalinizing the urine with NaHCO3

Amphetamine (weak base) overdose: excretion increased by acidifying the urine with NH4Cl

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Tubular reabsorption [active]

Sodium, glucose, amino acids, etc. in the GF are reabsorbed by tubular epithelium (carrier-mediated active transport).

Very few drugs are substrates for carriers involved in the active reabsorption of glucose, sodium, and amino acids from urinary filtrate.

The waste product uric acid can be reabsorbed by a carrier-based system. This carrier represents a drug target for patients with gout secondary to hyperuricemia.

Treatment of gout: “Uricosuric” agents including probenecid and aspirin block reabsorption of uric acid by saturating uric acid carriers.

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Tubular secretion
Tubular secretion II

Drugs can be secreted from blood to lumen of nephron through carriers.

Two separate carrier-mediated systems for bases and acids.

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

Acids: salicylate, penicillin, probenecid, conjugates of glucuronic acid and sulfate, etc.

Tubular Secretion II

Follows carrier-type kinetics (saturated at high drug concentration)

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

Penicillin secretion is readily blocked with Probenecid.

Only free drug is a substrate for carrier-mediated tubular secretion (however, the process of tubular secretion is not considered to be inhibited by high drug protein binding).

Renal Drug Clearance I

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

Clearance \( [CL] = \frac{U \cdot V}{P} \)

\( U \) = urine drug concentration (mg/ml)

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

\( V \) = rate of urine flow (ml/min)

Renal Drug Clearance II

If Renal drug clearance > GFR (> 130 ml/min).

The drug is primarily secreted (net effect).

Example: PAH [para-aminohippuric acid].

Renal clearance of PAH

\( CL = \frac{U \cdot V}{P} \)

\( CL = \left[65 \text{ mg/ml}\right] \left[1 \text{ ml/min}\right] / \left[0.1 \text{ mg/ml}\right] = 650 \text{ ml/min} \)

The renal clearance of PAH provides a measure of renal plasma flow

Renal Drug Clearance III

If Renal clearance < GFR then drug is:

Primarily reabsorbed by the Kidney (net effect).

\( CL = \frac{U \cdot V}{P} \)

\( CL = \left[50 \text{ mg/ml}\right] \left[1 \text{ ml/min}\right] / \left[1 \text{ mg/ml}\right] = 50 \text{ ml/min} \)

Renal Drug Clearance IV

If renal drug clearance = GFR (130 mL/min).

Drug is not secreted or reabsorbed and glomerular filtration is the primary mechanism.

Example: Creatinine and inulin.

Urinary creatinine clearance

\( CL = \frac{U \cdot V}{P} \)

\( CL = \left[130 \text{ ml/min}\right] \left[1 \text{ ml/min}\right] / \left[1 \text{ mg/ml}\right] = 130 \text{ ml/min} \)

Creatinine or inulin clearance provide a measure of GFR
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.
- Hepatic artery brings drugs to liver from systemic circulation
- Blood passes across cell plate formed by bilayer of hepatocytes.
- CV is surrounded by cell plate.
- BCM secretes various agents into bile.
- TBD connects lobule with gall bladder.

Hepatic Drug Clearance I

Drugs taken up by the liver classified by how efficiently they are removed.
- Two types of hepatic drug clearance patterns for drugs: High extraction and Low extraction
- High Extraction Ratio Drugs are efficiently cleared (near 100%) from blood during a single pass through the liver
  - Concentration in hepatic venous blood near zero.
  - Examples: Propranolol, Lidocaine and Morphine
- Clearance limited by blood flow more than by amount of enzyme
- Clearance of HER drugs is lower in elderly (reduced rates of blood flow, reduce dose).

Hepatic Drug Clearance II

Low Extraction Ratio Drugs are much less readily cleared from blood during single pass through liver.
- Concentration in blood leaving liver only slightly lower than concentration that comes into the liver.
- Examples: Tolbutamide, Warfarin, Phenobarbital
- Clearance limited more by amount of enzyme available to metabolize drug (affected by inhibitors, inducers/etc): blood flow is less important.
- Clearance of LER drugs lower in newborn and elderly (reduced rates of metabolism, lower dose).

Biliary Drug Excretion I

In addition to metabolism, the actions of drugs can be terminated by biliary excretion.
- Drug transporters in canalicular membrane of the hepatocyte excrete drugs and drug metabolites into the bile.
- Normal constituents of bile: Na, Bile Acids, PL and Cholesterol.
Biliary drug excretion II

Also secreted into bile:
- Organic acids (indocyanine green and BSP, bilirubin, various drugs and especially phase 2 conjugates of drugs (high MW))
- Organic bases
- Saturability, competition → dose-dependent elimination, drug interactions

Biliary Drug Excretion III

Biliary excretion can result in locally high concentrations of drugs in the intestinal lumen and can contribute to gastrointestinal toxicity (indomethacin, other drugs).

Enterohepatic Circulation of Drugs

Drugs or drug conjugates can be secreted into bile
- Drugs can be reabsorbed
- Prolongs duration of action.
- Drug conjugates (glucuronides/sulfates) can be hydrolyzed and drug reabsorbed in the lower GI
- Cycling can be inhibited by cholestyramine

Gastrointestinal Excretion of Drugs

Most orally administered drugs are not 100% absorbed → remainder in feces
- pH trapping can contribute to GI excretion
- Stomach (pH 1-3) traps bases (codeine) that diffuse into the stomach fluid from the blood
- Intestine (pH 6-8) traps acids (aspirin)

Pulmonary Drug Excretion

Blood air partition coefficient = \( \lambda \)
= [Drug in Lung Blood] / [Drug in Lung Air]
- Low \( \lambda \) drugs such as Nitrous Oxide (\( \lambda = 0.5 \))
  - Short duration of action and rapid elimination.
- High \( \lambda \) drugs such as methoxyflurane (\( \lambda = 12 \))
  - Long duration of action and slow elimination.
- Elimination rate inversely proportional to \( \lambda \)

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).