PHARMACOKINETICS: Elimination (p.1)

Concept of (plasma) "half-life"

A time measurement, which **starts when the drug reaches equilibrium** ("equilibrium" = "fully absorbed" = when equal amounts of drug are in circulation and at point of administration)

½ life = how much time it takes for blood levels of drug to decrease to half of what it was at equilibrium

thus, there are really two kinds of ½ life…

***"distribution"* ½ life** = when plasma levels fall to half what they were at equilibrium due to distribution to/storage in body's tissue reservoirs

***"elimination"* ½ life** = when plasma levels fall to half what they were at equilibrium due to drug being metabolized and eliminated

while both ½ lives contribute to the effects of the drug on behavior, it is usually the **elimination ½ life** that is used to determine dosing schedules, to decide when it is safe to put patients on a new drug, etc.

"Rule of Five"

generally, **5x the elimination ½ life** = time at which the drug is "completely" (97%) eliminated from the body (assuming that the drug was given in a **single** original dose

1x ½ life - 50% of the original drug removed
2x ½ life - 75%
3x ½ life - 87.5%
4x ½ life - 93.75%

5x ½ life - 96.875%

PHARMACOKINETICS: Elimination (p.2)

Drug metabolism/biotransformation

This mainly occurs in the liver, via liver enzymes

But it can also occur in the blood plasma or at various other places (stomach, intestines, lungs, skin, or kidneys) directly by various enzymes at those locations

In any case, these metabolites are then excreted/eliminated (more easily than would the parent molecule have been)
metabolites are often smaller in size, ionized

note: some drugs are excreted/eliminated in **unmetabolized form**, as the original drug molecule (e.g. Lithium)

How is drug (metabolite usually) actually excreted/eliminated?

Kidneys – in urine
Intestines – in feces
Lungs – in exhaled breath
Skin – in sweat
Also in bile (in feces), saliva, breast milk, tears, semen, hair, nails, etc.

The Kidneys

This is the **main excretory organ for drugs**

Arterial blood flows past the **nephron** (a web of tubules & blood Vessels)

Molecules (e.g. drug metabolites) leave arterial blood and enter the nephron tubules

If the molecule remains in the nephron tubules, then it will be excreted in the urine (about **2 qts. produced/day**)

If the molecule gets reabsorbed back into the returning venous blood it will be returned to general circulation (and can again have an effect at the RS if it reaches a RS)

About **190 qts. of fluids/day are processed** through the tubules,

most of which is reabsorbed
About 20% of blood plasma at any given time is being filtered
Kidneys filter > 1 liter/minute of fluids

PHARMACOKINETICS: Elimination (p.3)

How do (drug) molecules enter the tubules?

Mostly by passive filtration, flowing down their concentration gradients, entering via pores in body capillary walls and tubule walls (pores < 40-50 angstrom units)

How do (drug) molecules get reabsorbed into the venous blood?

Mostly by **active transport** (of ionized molecules)
Some by passive diffusion of non-ionized molecules (esp. if lipid soluble)
Some by selective diffusion through specific pores (non-ionized molecules)
note: to keep a lipid-soluble, non-ionized molecule in the tubules (in the urine) it would be best to change it into an ionized form which is then no-longer lipid soluble
can use "**ion-trapping**" here…if make urine acidic, will trap basic molecules, if make urine basic, will trap acidic molecules (**unalikes --- ionization**)
urine's pH ranges usually from 4.5 to 7(neutral) or 8 (slightly basic) so it usually traps bases

Other Routes of Excretion/Elimination:

In bile (which then empties into gut, excreted in feces)
1 liter/day of bile empties into duodenum
can excrete from 5 to 95% of drug dose, esp. **antibiotics**
water-soluble molecules get trapped in GI tract (esp. bases)…why?
lipid-soluble molecules may be reabsorbed from gut again and enter bloodstream

In sweat, saliva, tears, exhaled breath, milk, hair, nails
Note: as heart rate increases --- pulmonary circulation --- which then increases amounts of breath exhaled --- more drug

eliminated

Note: metabol/elim generally **slower in newborns & elderly** vs. adults
Note: metabol/elim in **healthy children/teens may be faster** than adults