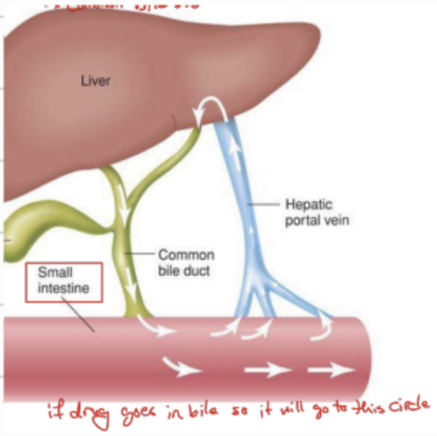
Entero Hepatic Cycling of Drugs : is recirculing of compounds between liver and intestine

liver → Common Bile duct → intestine → reabsorbtion → portal vain → liver



* Enterohepatic cycling
  - reduce Bioavailability
  - prolongs lifetime of elimination.

* there are many application on this cycle :
  - we take advantage of it in drug over dose ⇒ Activated Charcoal Can Absorb Drug and chemicals but it should be (not ionized) in to it's surface.

So in overdose with Drug that undergo this Cycle, we can trapped it in the gut and prevent reabsorbtion of it back to the circulation. ⇒ acceleration of Drug elimination

* Some properties of Drugs : features of the drug that depend only on the drug it self (not dose, not concentration)
  - Volume of Distribution (Vd)
  - Drug clearance (CL) — we will take about it later

Volume of Distribution (Vd) : is the size of Body fluid that would Be required if the drug molecules were to be Homogeneous distributed through all part of the Body (so it is the volume requierd to contain the drug to be the same Conc. in Blood.)

* Because this clause (in purble) the Vd will never show us the Real Volume, it show us the apparent Volume available in tissue of Distribution

$$* \quad V_D = \frac{Ab}{Cp}$$

Ab ↑ the available amount of Drug in the Body

Cp ↓ Concentration of Drug in Blood

* in normal 70 kg man.

Plasma	= 2.8 L	Aspirin	= 11 L
Blood	= 5.6 L	Ampicillin	= 20 L
ECF	= 14 L	Phenobarbital	= 40 L
TBW	= 42 L	Digoxin	= 640 L
Fat	= 14 - 25 L	Imipramine	= 1600 L
		Chloroquine	= 13000 L

* So How these drugs will distribute ?

Answer: the exess of Distribution Volume of Drug give me an indicator that it's absorbed in tissues

* Digoxin ⇒ 640 L But the Total Body water is 42 So it is highly distributed in tissue

↓ Vd = ↓ Distribution in tissue = ↑ drug restricted to plasma

Highly ionized in plasma pH → Binding to plasma protein (mostly reversable)
- α_1-acid glycoprotein → Bind to Basic drugs
- Albumin → most important one → Bind to acidic and Basic drugs

Drug + Protein ⟷ Drug-Protein complex

D + P ⟷ DP → Bound drug: represent reservoir for the drug

D + P → Unbound drug → which is effective (responsible for pharmacological action)
→ which eliminated in liver and other organs

* One clinical importance of plasma protein Binding of drugs is to help interpretation of measured plasma drug Conc. of such Drug.

So if the plasma protein Conc. is lower than normal ⇒ total drug concentration will be lower (which will be measured)

But the Bio available (unbound one) may Be normal

* plasma protein Binding is site of drug-drug interaction (as aspirine – Bilirubin) → مه كيسي

So if Drug display from plasma protein it will increase unbound drug ⇒ increase effect and maybe will be toxic

* Displaced Drug from plasma will be distribute throughout Volume of Distribution and it's rate of elimination is also increase so plasma Drug will not increase Dramaticlly. when the drug changed from bound → Unbound, it will be undergo Volume distribution and elimination (so this drug part will NOT goes Totatally to the tissues → plasma drug Conc. will NOT increase dramatically (but it will increase).

* Drug Clearance: Volume of Blood or plasma that is completely cleared of Drug By Time Unite

↓ By two ways:
- → distribution to tissues
- → elimination of Drug By:
  - hepatic execretion
  - renal execretion

* Clearance of the drug is the factor that predicts the rate of elimination in relation with conc.

$$CL = \frac{\text{rate of elimination}}{\text{Conc of Drug in plasma}}$$

, and there is more than one method of elimination so there

So the rate of eliminatio is the sum of All elimination methods

$$\text{Renal Clearance} = \frac{C_u \cdot V}{C_p}$$

- C_u → drug Conc. in urine
- V → Volume / time
- C_p → Conc. of drug in plasma

$$\text{Hepatic Clearance} = \text{Blood flow} \frac{(C_i - C_o)}{C_i}$$

- C_i is Concentration of blood going to liver
- C_o " " " " going out from liver
- Blood flow: reffered to it By Q (90 L/H in healthy people with 70 kg)

$\frac{C_i - C_o}{C_i}$ ⇒ ER (extraction Ratio of Drug)

$$* ER = \frac{\text{Hepatic Clearance}}{Q}$$

* Bioavailability (F) = extent of absorbtion (f) · (1 − ER)

* Morphine is completely absorbed but it's ER = 0.67 so it's Bioavailability 0.33

* there are differences in hepatic Blood flow and drug metabolism so it will cause differences in Bioavailability interindividual differences in drugs with high extraction ratio

Calculation Questions:

① 500 mg of Drug X was given to patient then you take a sample of His Blood and see that the drug conc is 100 mg/L what the V_D of this Drug ?

Ans: $V_D = \frac{\text{Amount (dose)}}{C_p} \Rightarrow \frac{500\ mg}{100\ mg/L} = 5\ L$

② Assume that the rate of elimination of Drug is 10 mg/hour and plasma Conc. is 1 mg/L what is drug clearance ?

Ans: $CL = \frac{\text{elimination}}{C_p} = \frac{10\ mg/hour}{1\ mg/L} = 10\ L/hour$

بتعرف شو هي نواقض لا إله إلا الله ؟

يعني شو الأشياء الي بتبطل الإسلام

ابحث عنها بس اكتب بقولك الي

لونه احمر راح يطلعلك

Done By: Abd Arrahman Dabbas