ای یاد تو مونس روانم

جز نام تو نیست بر زبانم

فارماکولوژی دامپزشکی

فارماکولوژی پایه

فارماکوکینتیک

دکتر گودرز صادقی

دانشیار فارماکولوژی

دانشکده دامپزشکی

Introduction

- Pharmacokinetics: A mathematical description of the time course of drug absorption, distribution, metabolism, and elimination.
- The goal of pharmacokinetic modeling:
  - To establish therapeutic drug doses and dosing regimens.
  - To establish drug withdrawal times for meat and milk in food animals.
- Important pharmacokinetic parameters:
  - Bioavailability, clearance, serum half-life ($t_{1/2}$), and volume of distribution (V_d).

Bioavailability- 1

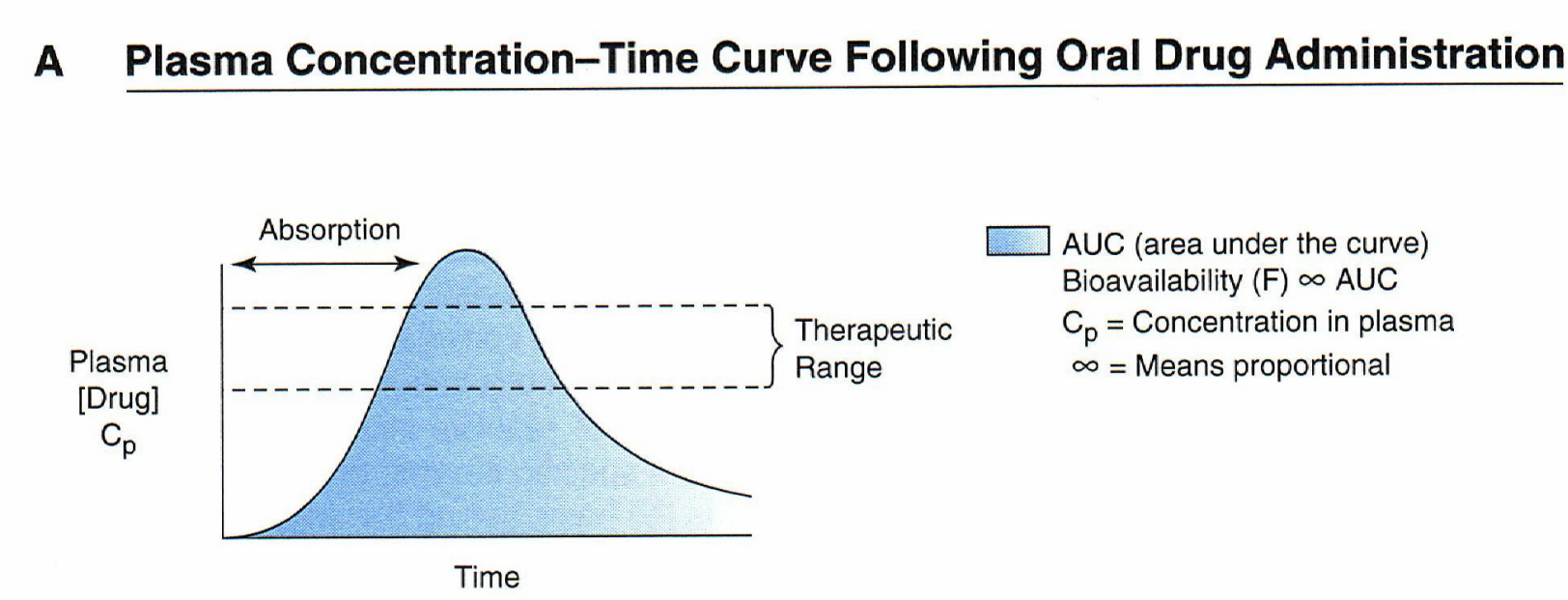
- Bioavailabilit*y:* for description of the rate and extent to which a drug reaches its site of action.
- Drugs given IV are essentially 100% bioavailable.
  - Other parenteral routes (IM or SC): Greater bioavailability than those given orally.
- The bioavailability by other routes: The fraction of the dose that reaches the blood circulation in an active form.
  - Any factor that affects drug absorption, influences drug bioavailability.

Bioavailability- 2

- Oral drugs
  - Bioavailability depends on: GI absorption + hepatic and GI metabolism
- The oral bioavailability of some drugs can be severely limited by extensive first-pass hepatic metabolism.
- In general, orally administered drugs should have a relatively high bioavailability, but in reality the reproducibility of absorption is more clinically important.

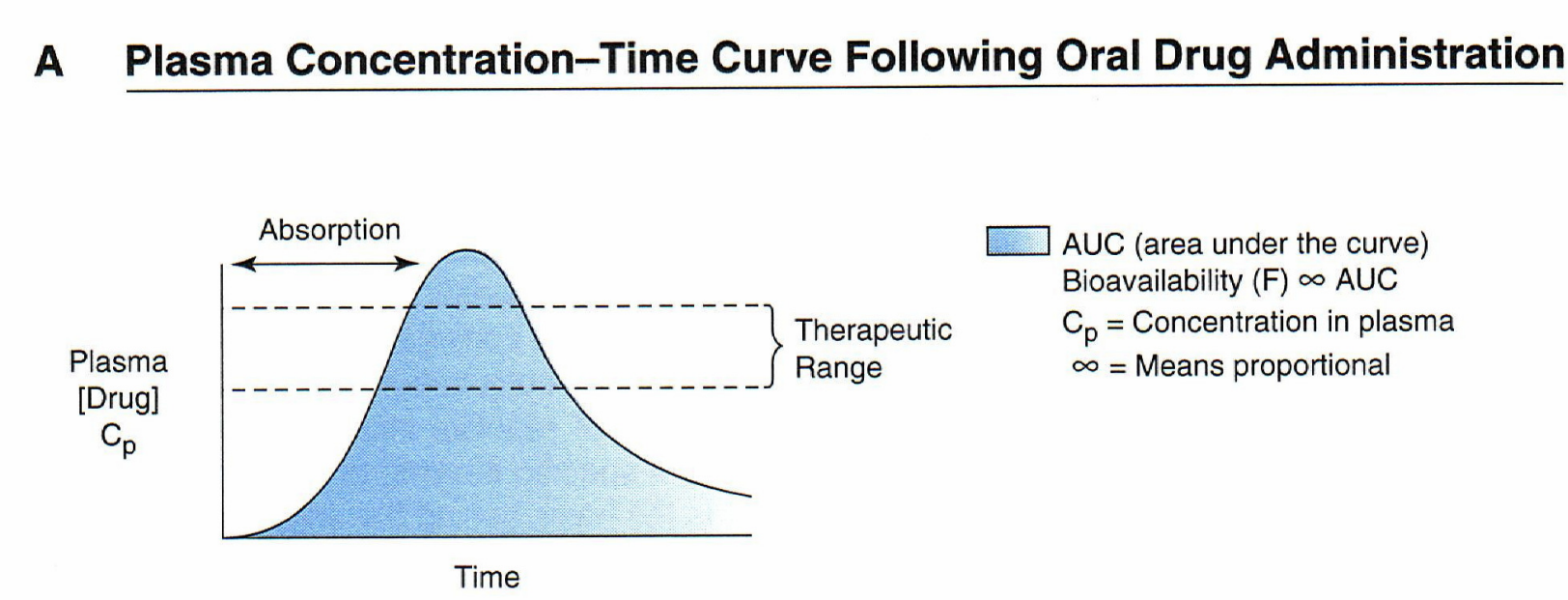
Bioavailability- 3

- Mathematically, bioavailability is represented by the AUC of a drug's plasma concentration-time curve.



Volume of Distribution - 1

- V_d: quantitative estimate of the extent of drug distribution.



Volume of Distribution - 2

- A theoretical volume in which the total drug would have to be uniformly distributed to give the observed Cp.
- A proportionality constant that relates the amount of drug in the body to the concentration of drug in the blood:
  - Vd = total amount of drug in the body / serum drug concentration at steady state (Css)

Volume of Distribution - 3

- If V_d = plasma volume: the drug is confined to the plasma $\Rightarrow$ not useful as a drug
- If V_d > plasma volume: the drug is localized outside the plasma
- High lipid solubility $\Rightarrow$ cell penetration $\Rightarrow$ distribution intra-cellularly $\Rightarrow$ a larger V_d than drugs confined to interstitial fluids

Volume of Distribution - 4

- The V_d reflects a drug's affinity for plasma and tissue binding.
- High levels of plasma protein binding $\Rightarrow \downarrow V_d$ to the plasma volume
- Binding to tissues $\Rightarrow \uparrow V_d$
- Highly lipid solubility $\Rightarrow$ slowly partitioning into adipose tissue $\Rightarrow \uparrow V_d$
- Adipose tissue has a low blood supply: Drug deposition in fat $\Rightarrow \uparrow$ drug accumulation
  - Obesity $\Rightarrow \uparrow$ the Vd of highly lipophilic drugs

Clearance - 1

- Clearanc*e:* the volume of blood cleared of a drug per unit of time
- Total clearance: the sum of clearances from each eliminating organ (liver, kidneys, and lungs)

Clearance = rate of drug elimination / serum drug concentration

Clearance - 2

- Clearance is important in determining dosage regimens required to produce a desired steady-state serum drug concentration (Css).
- Css is established when clearance = the rate of drug administration.

Dosing rate = clearance / steady-state serum concentration of drug

Clearance - 3

- Clearance is constant over a range of drug doses as long as the systems for drug uptake and elimination are not saturated
  - First-order kinetics: A constant fraction of the drug is eliminated per unit of time.
- When any component of drug uptake or elimination becomes saturable:
  - Zero-order kinetics: A constant amount of drug is eliminated per unit of time $\Rightarrow$ clearance becomes variable.

Clearance - 4

- Clearance may be influenced by:
  - Plasma protein binding
  - Organ perfusion
  - Drug-metabolizing enzyme ability
  - The efficiency of renal excretion.
- A drug bound to plasma proteins is not filtered at the glomerulus.
  - If drug excretion by filtration is the major mode of elimination from the body, changes in the extent of protein binding can affect the rate of renal clearance.
  - Plasma protein binding does not alter the clearance of drugs that are metabolized by the liver and excreted in the bile.

Clearance - 5

- Clearance will vary depending on the drug hepatic extraction ratio (HER).
  - The hepatic extraction ratio is the fraction of drug presented to the liver that is cleared after a single pass through the liver.
- If >70% of a drug is extracted by the liver in one pass, the drug is said to have a high HER (propranolol, diltiazem, chlorpromazine).
  - Clearance of this drug is described as blood flow limited and any factor that alters hepatic blood flow will affect drug clearance.

Clearance - 6

- If HER 30% (most drugs): clearance is closely tied to free drug concentration.
- Now changes in plasma protein binding or in the intrinsic ability of the organ to metabolize the drug will have a greater effect on total clearance.

Plasma Half Life ($t_{1/2}$) - 1

- $t_{1/2}$: The time it takes for the total amount of drug in the body to decrease by 50%.
- It gives an estimate of the duration of drug effects in the body.
- The $t_{1/2}$ is a derived parameter dependent on both clearance and Vd.

$$t_{1/2} = 0.693\ Vd / clearance$$

Plasma Half Life ($t_{1/2}$) - 2

- Diseases alter clearance and Vd independently $\Rightarrow$ $t_{1/2}$ is an unreliable indicator of elimination.
- Some compounds may have similar clearances, but very different $t_{1/2}$ values.
  - Ampicillin and digoxin have similar clearances
  - They differ Vd
  - $t_{1/2}$ of Ampicillin = values of 48 min
  - $t_{1/2}$ of Digoxin = 1,680 min

Plasma Half Life ($t_{1/2}$) - 3

- $t_{1/2}$ is a useful parameter for the determination of:
  - The amount of time required to reach steady-state drug concentrations (about 4 x $t_{1/2}$)
  - The time it takes for a drug to be removed from the body (50% should be eliminated in each $t_{1/2}$).
  - A means to estimate dosing interval

Home Page

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خدایا چنان کن سرانجام کار تو خشنود باشی و ما رستگار