كلية الصيدلة
College of Pharmacy
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Biopharmaceutics
Course #414:

DRUG ELIMINATION AND CLEARANCE

UOBCOP
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Drug Clearance

- *Drug clearance* is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process.

$$Cl_T = \frac{elimination\ rate}{C_p}$$

$$Cl_T = \frac{dD_E/dt}{C_p} = \quad \text{ml /min}$$

- D_E= amount of drug eliminated
- D_E/dt= rate of elimination

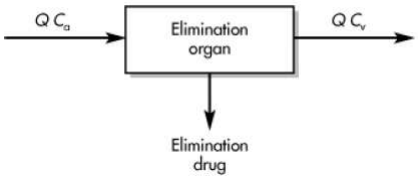
$$Cl_T = \frac{kC_p V_D}{C_p} = kV_D$$

Total body clearance (Cl_T)

$$\text{Renal clearance} = k_e V_D$$
$$\text{Lung clearance} = k_l V_D$$
$$\text{Hepatic clearance} = k_m V_D$$
$$\text{Body clearance} = k_e V_D + k_l V_D + k_m V_D$$
$$= (k_e + k_l + k_n) V_D = k V_D$$

Clearance Models

- **Physiologic/Organ Clearance**



- Q = blood flow,
- *C* a = incoming drug concentration [usually arterial drug concentration],
- *C* v =outgoing drug concentration [venous drug concentration]).

The clearance of drug by any organ or tissue

Cl=Q (ER)

- Q= blood flow
- ER= the extraction ratio (ER with no unite ranges from 0 -1)

$$\mathrm{ER} = \frac{C_a - C_v}{C_a}$$

$$Cl = Q\left(\frac{C_a - C_v}{C_a}\right)$$

- (C a)=drug concentration entering the organ
- (C v)=drug concentration leaving the organ

RENAL CLEARANCE

Renal clearance (Cl_R) is defined as the volume of plasma that is cleared of drug per unit of time through the kidney

$$Cl_R = \frac{Q_u C_u}{C_P} = \frac{\text{excretion rate}}{C_P}$$

Cl_R = renal clearance,
C_p = plasma drug concentration,
Q_u =the rate of urine flow
C_u =the urine drug concentration.

Comparison of Drug Excretion Methods through the renal system

$$Cl_R = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{C_p}$$

Comparison of Drug Excretion Methods

FILTERATION ONLY

Cl R = GFR

$$k_e = \frac{Cl_R}{V_D}$$

FILTRATION AND REABSORPTION

For a drug with a *reabsorption fraction* of *fr*, the drug excretion rate is reduced

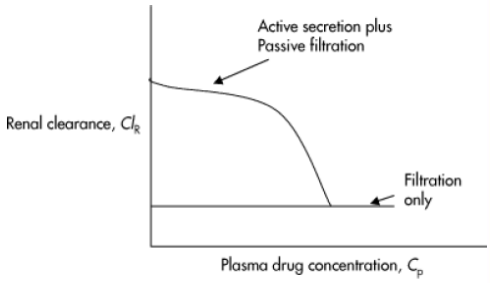
Cl R < GFR

$$\frac{dD_u}{dt} = Cl_R(1 - fr)C_p$$

(*fr*)=The reabsorption fraction

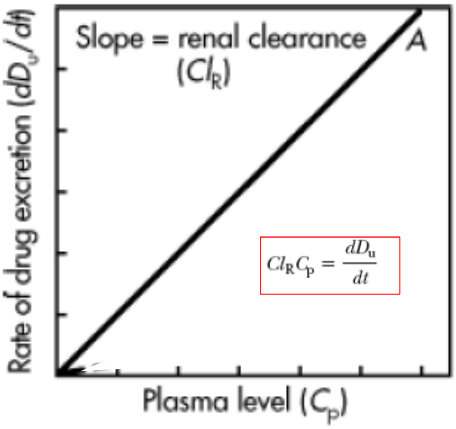
FILTRATION AND ACTIVE SECRETION

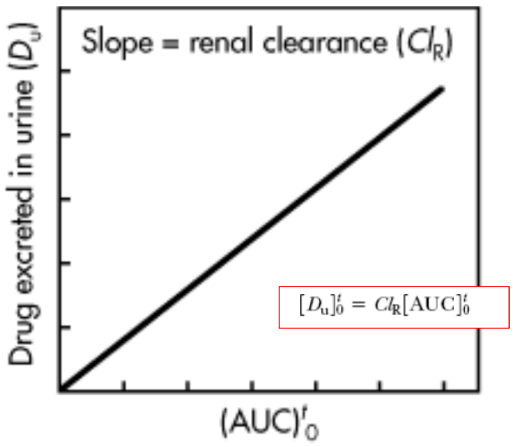
For a drug that is primarily filtered and secreted, with negligible reabsorption, the overall excretion rate will exceed GFR. (*Cl* R >GFR)



the decline of renal clearance. As the drug plasma level increases to a concentration that saturates the active tubular secretion, glomerular filtration becomes the major component for renal clearance

DETERMINATION OF RENAL CLEARANCE
1- Graphical Methods:





Cumulative drug excretion versus AUC. The slope is equal to *Cl* R
[Du]=cumulative drug excreted in the urine

2-Model-Independent Methods

$$Cl_T = kV_D$$
$$Cl_R = k_e V_D$$
$$Cl_h = k_m V_D$$

Cl T=Cl $_R$+Cl $_h$

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Model-Independent Methods

- Model-independent methods are noncompartment model approaches used to calculate certain pharmacokinetic parameters such as clearance and bioavailability (F).
- The major advantage of model-independent methods is that:
  - no assumption for a specific compartment model is required to analyze the data.
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  - no assumption for a specific compartment model is required to analyse the data.
  - the VD & (k)need not be determined directly from the equation that best fits the plasma drug concentration–time curve.
  - Clearance can be determined directly from the plasma–time concentration curve by

$$Cl_r = \frac{D_0}{[\mathrm{AUC}]_0^\infty}$$

Because $[AUC]^{\infty}_{0}$ is calculated from the plasma drug concentration–time curve from 0 to infinity using the trapezoidal rule, no compartmental model is assumed

3-Calculation of Clearance in Multicompartmental Models

$$Cl_T = kV_p \qquad (6.42)$$

or, alternatively,

$$Cl_T = bV_{D_\beta} \qquad (6.43)$$

To obtain renal clearance for drugs demonstrating two-compartment kinetics with metabolism and excretion, the following equation is used:

$$Cl_R = k_e V_p \qquad (6.44)$$

b =the elimination rate constant

VD_B= **The volume of distribution by area,**

Fraction of Drug Excreted

Fraction of drug excreted unchanged in the urine

$$= f_e = \frac{D_u^\infty}{FD_0} = \frac{k_e}{k} \qquad (6.45)$$

$$Cl_R = \frac{D_u^\infty}{FD_0} Cl_T = f_e Cl_T \qquad Cl_R = \frac{k_e}{k} Cl_T$$

$D_{\infty u}$ = the total amount of unchanged drug excreted in the urine,
$FD_{0=}$ the fraction of the dose absorbed,
$f_{e=}$ the fraction of drug excreted unchanged in the urine

Total Body Clearance of Drugs after Intravenous Infusion

- Cl_T=R/Css
  - *C* SS = the steady-state plasma drug concentration
  - *R* =the rate of infusion.
  - This equation is valid for one or two compartment model.

Hepatic drug metabolism

- The elimination =metabolism (biotransformation)+renal excretion
- Sites for drug metabolism are:
  - liver. (most drugs are metabolized by liver)
  - the lung,
  - skin,
  - gastrointestinal mucosal cells,
  - microbiological flora in the distal portion of the ileum, and large intestine.
  - The kidney .

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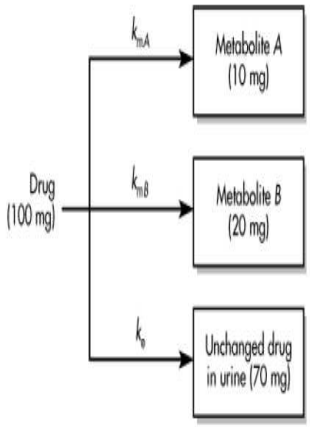
- Knowledge of the fraction of the drug that is eliminated by metabolism and the fraction of drug that is eliminated by excretion is useful information that helps to:
- predict whether a change in drug elimination is likely to be affected by renal disease, hepatic disease, or a drug–drug interaction.

First-Order Elimination

- Km=k-ke
- A drug may be biotransformed to several metabolites (metabolite A, metabolite B, metabolite C, etc);
- thus,
  - (*k* m) =Km=kmA+kmB+kmC…..+kmI

$$\% \text{ drug metabolized} = \frac{k_m}{k} \times 100$$



Assuming the metabolism is 1st order kinetics

Fraction of Drug Excreted Unchanged (*fe*) and Fraction of Drug Metabolized (1–*fe*)

$$\boldsymbol{fraction\ of\ drug\ execreted\ unchanged = fe = \frac{ke}{k}}$$

Fraction of drug metabolized =1-f

$$\frac{k_e}{k} = \frac{\text{total dose excreted in urine}}{\text{total dose absorbed}} = \frac{D_u^\infty}{FD_0}$$

- the percent of drug eliminated by renal excretion:
  - % drug execration $=\frac{ke}{k}*100$ or $\frac{D_u}{D_0}*100$
- The percentage of drug metabolized
  - % of metabolized drug=% 100- % drug excretion

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Practical example

K=0.347hr-1, Km=0.104 hr-1

T1/2=0.693/0.347 hr-1➔ t1/2= 2 hrs

The elimination constant if the renal is not impaired.

- *If the renal excretion is totally impaired ➔ ke~0*
- The $t_{1/2}$ can be determined as follows:
- K=km+ke
- K=km = 0.104
- t ½ =0.693/k
- ➔=0.693/0.104 =6.7 hrs.
- The t1/2 is changed form 2 hrs to 7 hrs in renal impairment
- The dose should be adjusted to prevent accumulation of toxic drug level

HEPATIC CLEARANCE

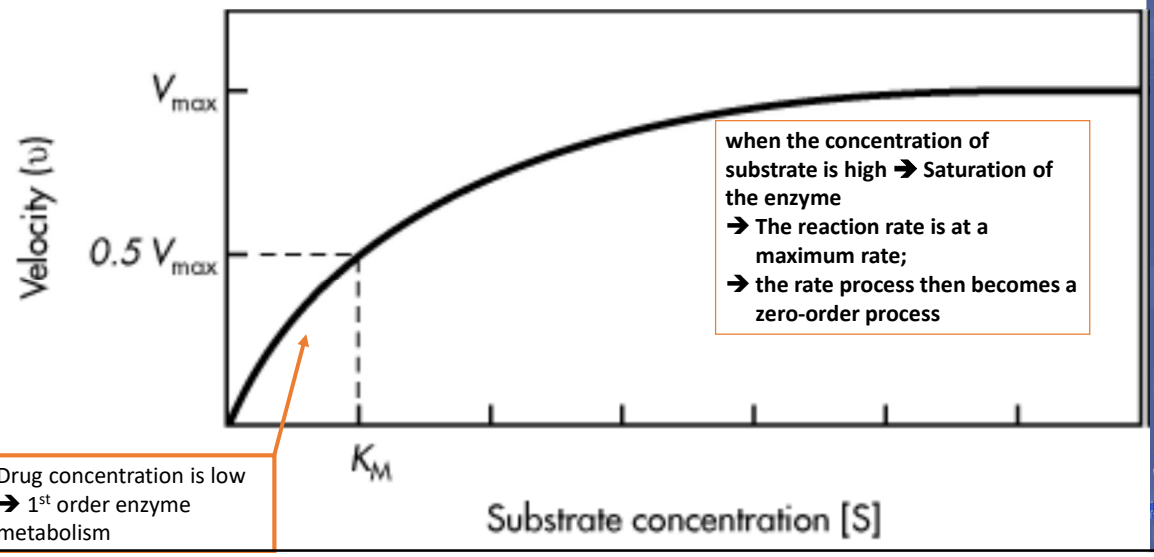
- *Hepatic clearance* may be defined as the volume of blood that perfuses the liver and is cleared of drug per unit of time
- $Cl_T=Cl_{NR}+Cl_R$

Extrahepatic Metabolism

- Morphine clearance, *Cl* T, for a 75-kg male patient is 1800 mL/min. After an oral dose, 4% of the drug is excreted unchanged in the urine (*f* e = 0.04). The fraction of drug absorbed after an oral dose of morphine sulfate is 24% (*F* = 0.24). Hepatic blood flow is about 1500 mL/min. Does morphine have any extrahepatic metabolism?

Solution:
Since *f* e = 0.04, renal clearance *Cl* r = 0.04 *Cl* T and nonrenal clearance *Cl* nr = (1 – 0.04) *Cl* T = 0.96*Cl* T. Therefore, ***Cl* nr = 0.96 x 1800 mL/min = 1728 mL/min**. Since hepatic blood flow is about 1500 mL/min, thedrug appears to be metabolized faster than the rate of hepatic blood flow. Thus, at least some of the drug must be metabolized outside the liver. The low fraction of drug absorbed after an oral dose indicates that much of the drug is metabolized before reaching the systemic circulation.

ENZYME KINETICS



ENZYME KINETICS

$$v = \frac{V_{max}[D]}{[D] + K_M} \qquad (11.20)$$

- The rate of metabolite formation
- (V_{max}) max velocity when the saturation of the enzyme is achieved.
- K_M =The *Michaelis constant,* ***(The K_M is a useful parameter that reveals the concentration of the substrate at which the reaction occurs at half V_{max})***
- V= the rate for the formation of the product (metabolite)
- [*D*] = drug concentration