PHARMACOLOGY

بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

MID – Lecture 4

Pharmacokinetics (Pt.3)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Written by:

- Muthanna Khalil
- Mohammad Mahasneh

Reviewed by:

- Saleh Alnaji

Quiz on Last Lecture

Bioequivalence ⇔ Comparative Bioavailability (F)

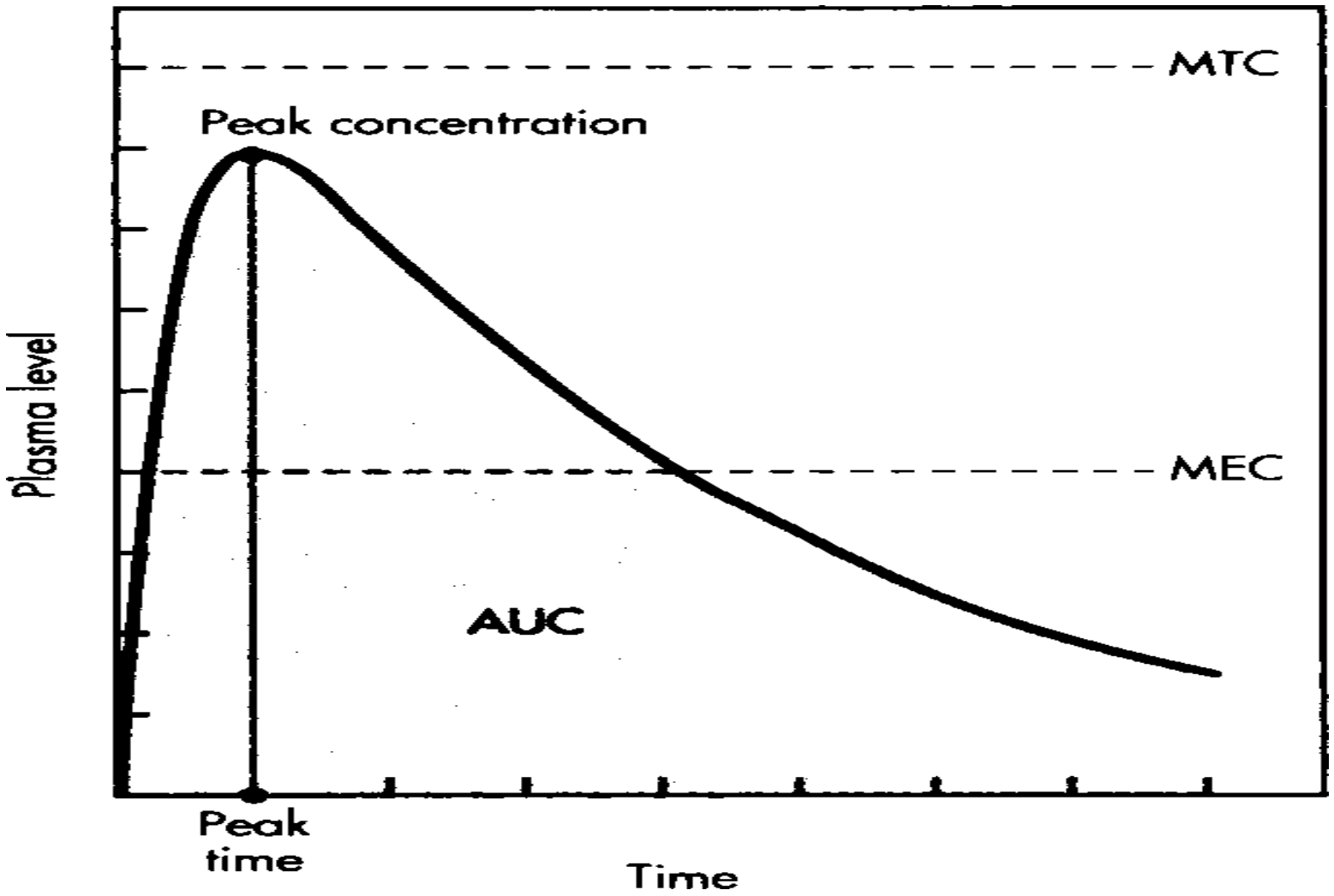
- **This term is used to compare the rate and extent of absorption of different formulations (or dosage forms) of the same active drug.**
- **The extent of absorption is measured by AUC, and the rate is assessed by C_{max} (peak concentration) and T_{max} (time to peak concentration).**

In pharmaceutical context, the drug that is first proven (by extensive research and trials) to have the appropriate and adequate therapeutic effect when given in specific doses is called the **originator** drug.

Bioequivalence tells us if any so-called "alternative" of the originator drug is actually a viable alternative usually by comparing the [Plasma concentration vs Time] curve of both (see next slides).

If the "alternative" is **adequately similar** to the originator, then it is a real alternative and is safe to use. Otherwise, the "alternative" is not really an alternative and the manufacturer should be held accountable.

Plasma Concentration vs Time (Part 1)

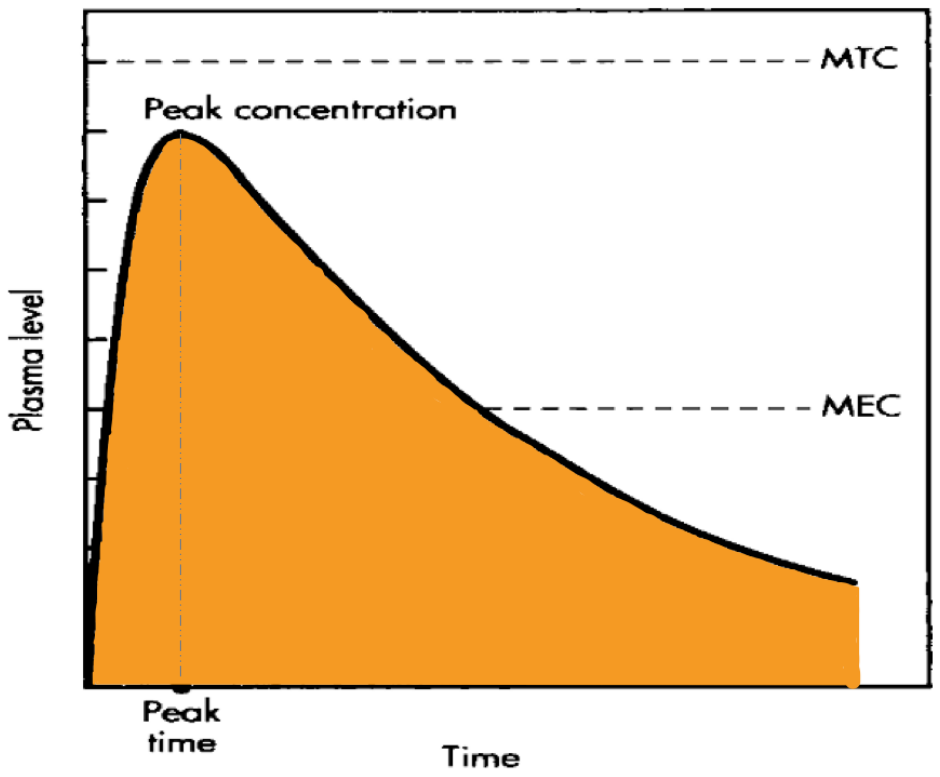


➔ Minimum Toxic Conc.

➔ Minimum Effective Conc.

This graph is extremely important (see next slides)

Plasma Concentration vs Time (Part 2)



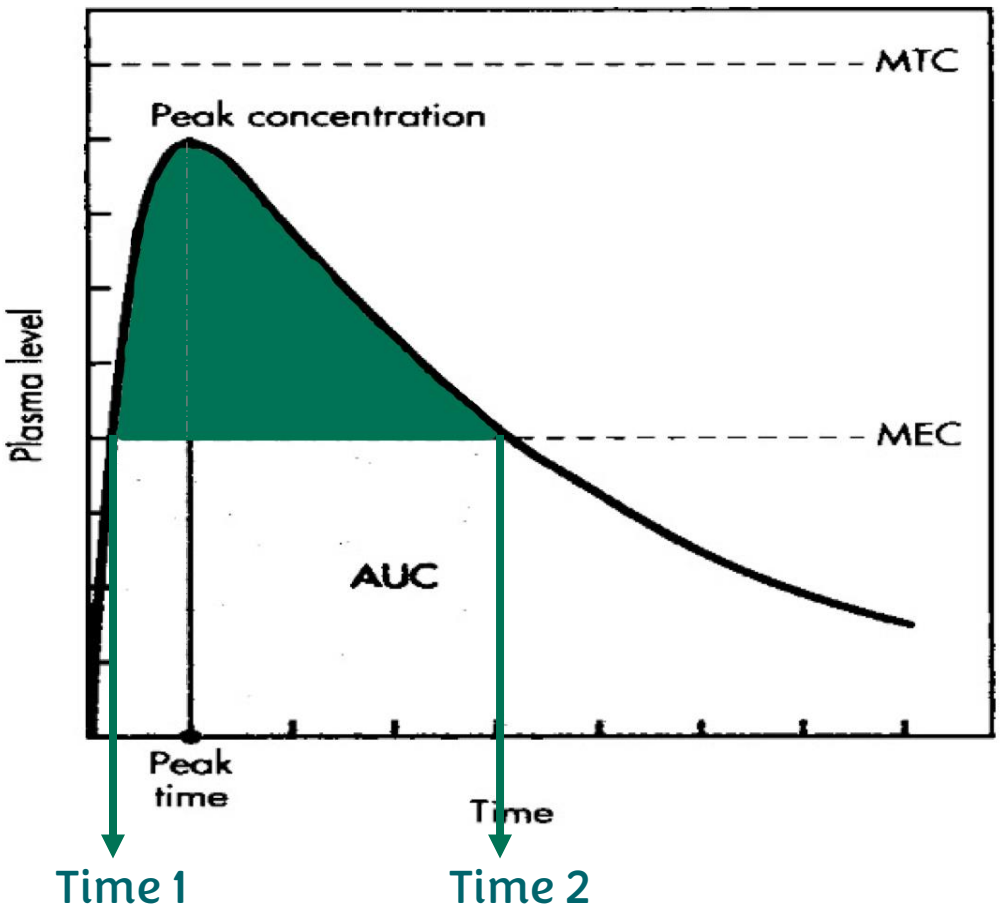
- Total Area Under the Curve (AUC)
- Total Drug **Exposure**
- Reflects the Extent of Bioavailability
- Time interval (x-axis):
  From administration to inactivation or elimination from the circulation.

- Recall that Bioavailability (F) is the fraction of the unchanged active drug reaching the **systemic circulation** following administration.
- Notice that we measure the drug plasma concentration, which is in the **systemic circulation.**

$$\textbf{\textit{Exposure}} = AUC = \oint \boldsymbol{C(t)}dt \; ; C(t) \text{ is the plasma concentration (as function of time)}$$

Notice the direct proportional relation → the higher the concentration, the higher the exposure.

Plasma Concentration vs Time (Part 3)



- AUC that is above the line of MEC
- Therapeutically active Drug Exposure
- The higher the C_{Peak}, the higher the effect
- Time interval (x-axis):
  From first reaching MEC to returning to MEC
  We call it the **duration of action of the drug**

For the best effect:

- The drug concentration must stay above MEC for sufficient time
- The drug concentration must stay below MTC to avoid toxic effects

$$Effect \rightarrow \boldsymbol{AUC}\ (above\ MEC) = \int_{Time\ 1}^{Time\ 2} (\boldsymbol{C(t)} - MEC)dt$$

➔ We can infer from the expression on the left:

1. For a given concentration, the wider the duration, the greater the pharmacological effect.
2. For a given duration, the higher the concentration, the greater the pharmacological effect.

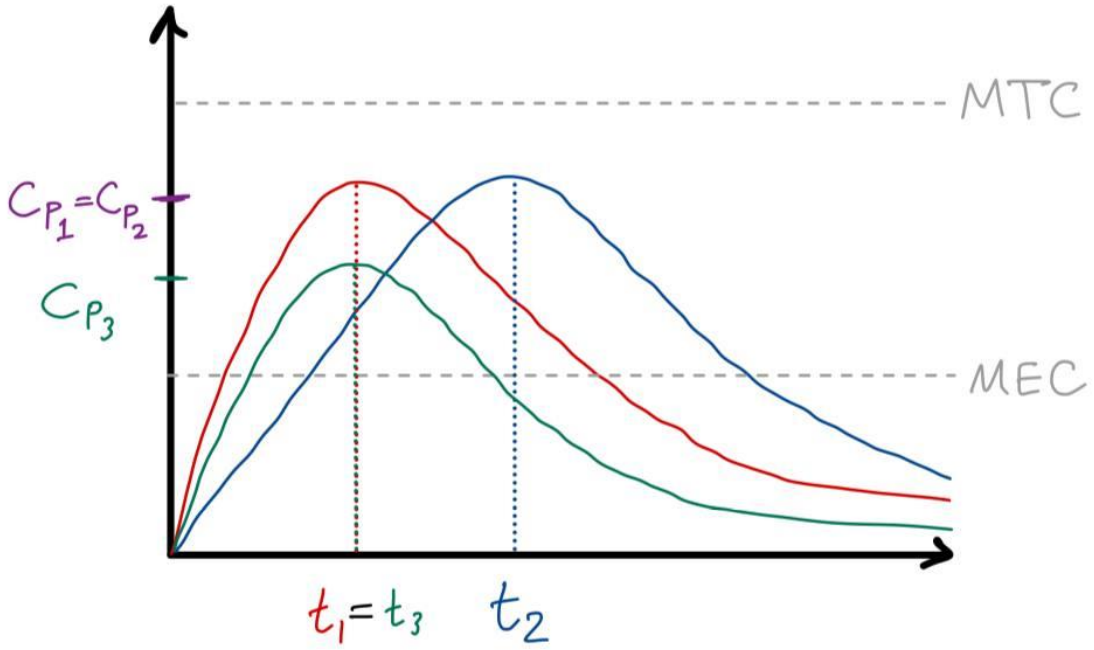
Plasma Concentration vs Time (Part 4)

Now we'll consider bioavailability rate, which is reflected by the **time required to reach the peak concentration.**

Suppose we have 3 drugs, where:

t_{peak} of 1 = t_{peak} of 3
t_{peak} of 2 → t_2

C_{peak} of 1 = C_{peak} of 2
C_{peak} of 3 → C_{P3}



Bioavailability Rate: $\frac{1}{t_{peak}}$

$For\ Drug\ 1 \rightarrow \frac{1}{t_{peak}} = \frac{1}{t_1}$

$For\ Drug\ 2 \rightarrow \frac{1}{t_{peak}} = \frac{1}{t_2}$

$For\ Drug\ 3 \rightarrow \frac{1}{t_{peak}} = \frac{1}{t_3}$

The rate is only affected by the t_{peak} $\{t_1, t_2, t_3\}$, irrespective of C_{peak}

Since it is an inverse relation,
Because $t_1 = t_3 < t_2$ → Rate 1 = Rate 3 > Rate 2

Now these 3 drugs (A, B, C):
Apply the same concepts from the previous slides.

Keep in mind that Drug A is the originator drug.

Read the captions below the figure.

Drug C is unacceptable because it has a slower rate, as well as a lower active exposure (AUC above TC).
- Violates Rate of Bioavailability.
- Not bioequivalent to Drug A.

Drug B is unacceptable because it does not reach TC → no therapeutic effect at all!
- Violates Extent of Bioavailability.
- Not bioequivalent to Drug A.

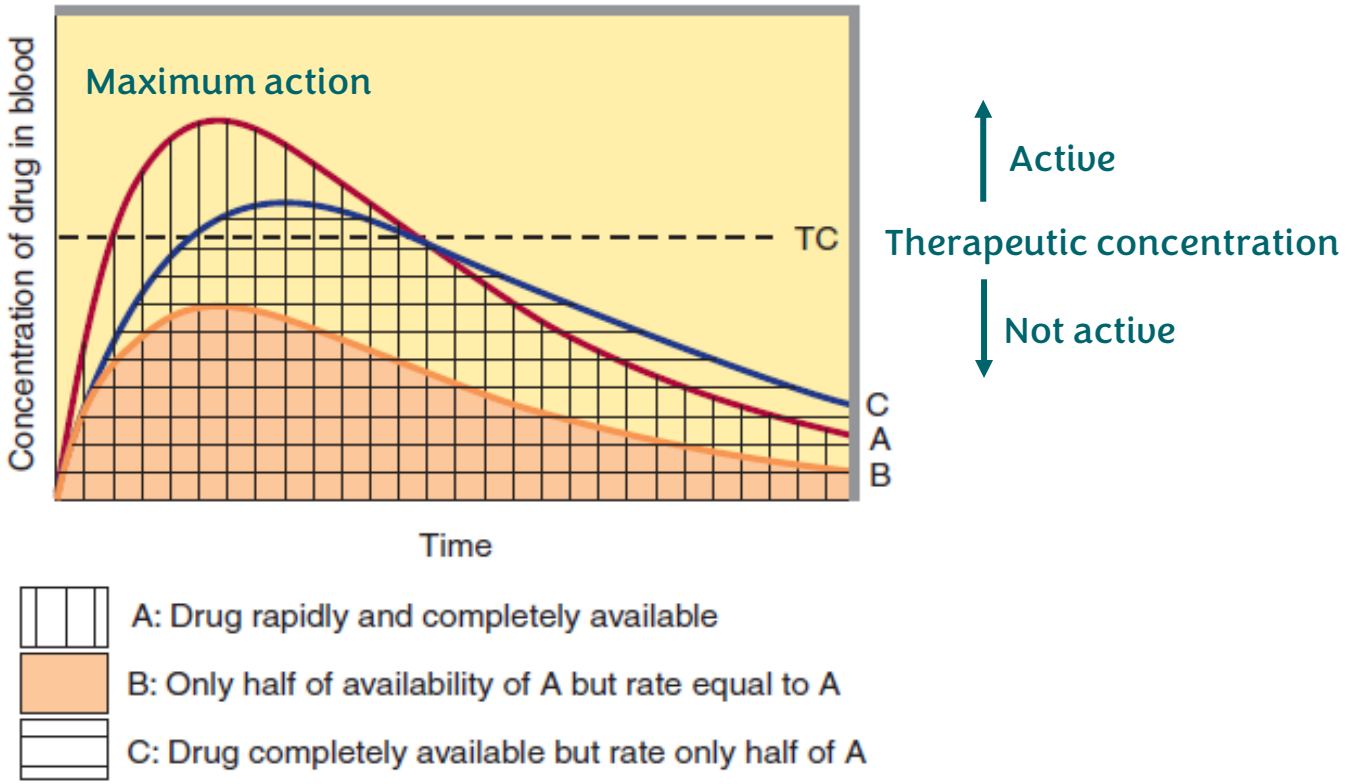
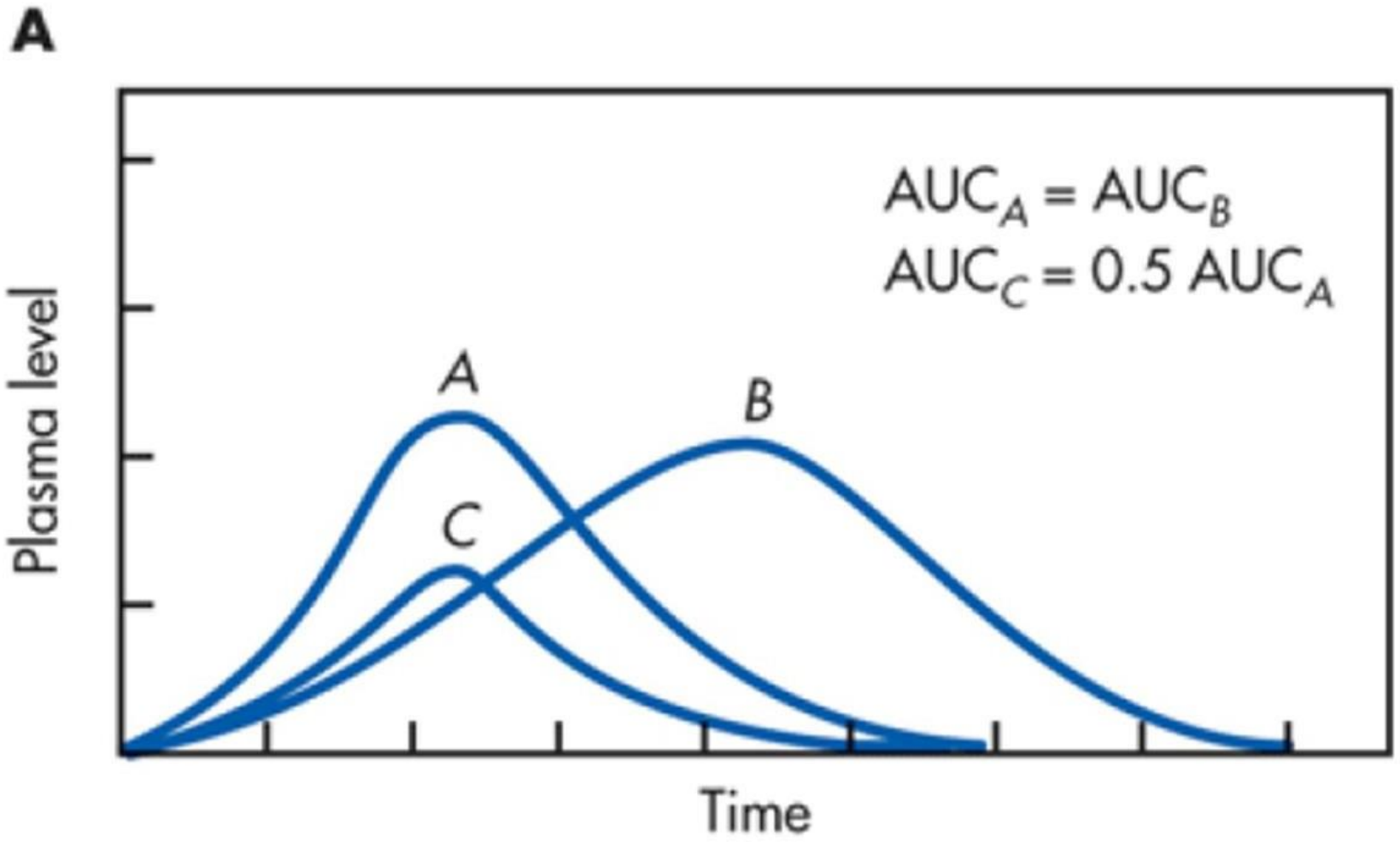


FIGURE 3-4 Blood concentration-time curves, illustrating how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations. The dashed line indicates the target concentration (TC) of the drug in the blood.

The correct approach in the case of Drug B, for example, is not to increase the dose (although it may then give the same effect as Drug A) but to make sure such drugs are no longer in the market since they indicate bad manufacturing and may induce severe adverse effects. Such low-quality formulations must not be used.



Drug C → not bioequivalent to Drug A.

Drug B → can be a good alternative if we don't need a well-timed response.

- It can be used as an alternative of Drug A only in non-critical cases.
- In critical conditions, such as in case of acute myocardial infarction, the patient may die before enough of the drug is bioavailable to cause the desired therapeutic effect.

Intestines Liver

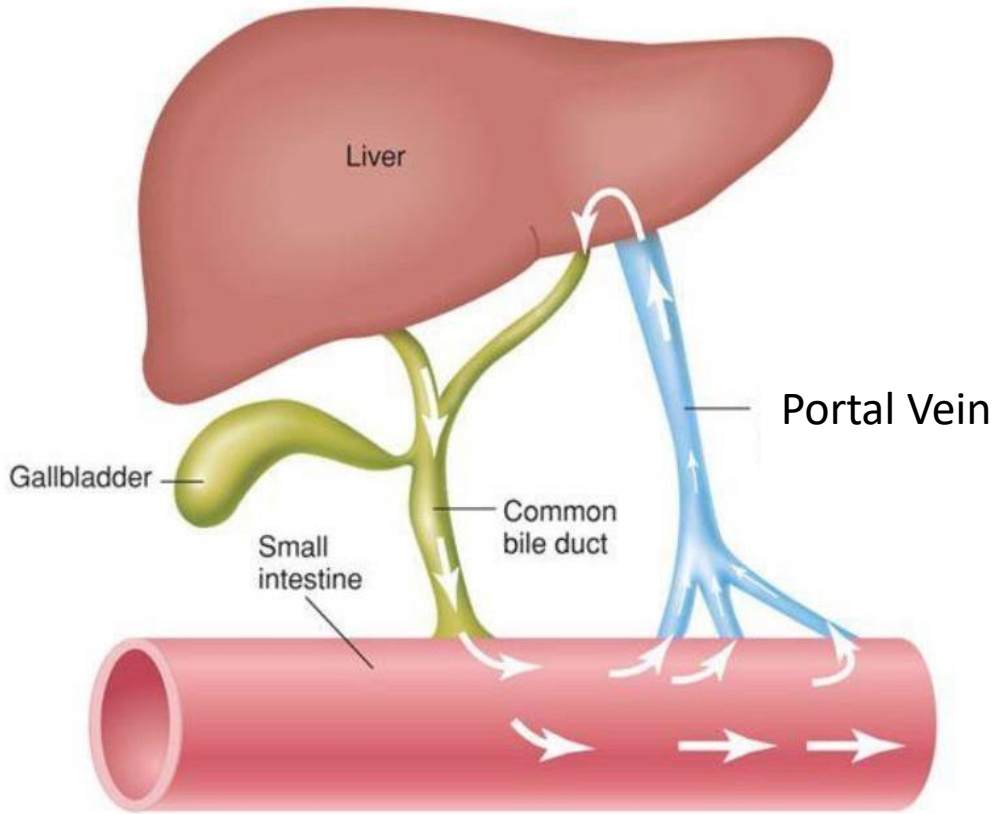
Enterohepatic Cycling of Drugs

- After oral administration and absorption, a drug can be excreted in bile before reaching the systemic circulation, go back to gut lumen, and then reabsorbed again.
- This is called enterohepatic cycling of the drug.
- It reduces drug bioavailability and prolongs its half-life of elimination.

The occurrence of this phenomenon depends on the properties of the drug.

Enterohepatic Circulation

- Is recirculation of compounds between liver and intestine
- Many compounds are released in bile, reabsorbed in SI, and returned to liver to be recycled
- Liver excretes drug metabolites into bile to pass out in feces



This phenomenon can affect any administration route where the drug eventually passes by the liver, so it is not only for oral administration.

For some drugs, the drug is metabolized by conjugation (adding of groups by dehydration for example), so when the drug reaches the intestines, it may get hydrolyzed, returning from the conjugated form to the active form which may be reabsorbed by the intestines into the portal vein and the cycle continues...

Enterohepatic Cycling of Drugs

Application:

- **This phenomenon can be taken advantage of in cases of drug overdose, to enhance drug elimination from the body.**
- **Activated charcoal can adsorb may drugs and chemicals (except ionized ones, and petroleum distillates) into its surface.**

adsorb ⇔ bind to

- The charcoal used for barbeque doesn't work ☺
- Even the tablets sold at pharmacies don't work for treatment of overdose, but it can work for some other mild problems because it contains a low efficacy form of the activated charcoal.
- The best approach is to let the patient drink activated charcoal powder in water.
- You should consider the appetizing aspects – add a flavor and don't use a transparent container.
- Sometimes you may need to use nasogastric or orogastric tube to deliver the activated charcoal to the stomach → intestines → it will adsorb the drug preventing absorption and enhancing elimination.

Enterohepatic Cycling of Drugs

- If we give activated charcoal orally in cases of drug overdose, and the drug undergoes enterohepatic cycling, then the portion of the drug that is excreted into the gut through bile can be trapped and prevented from reabsorption back into the systemic circulation.
- This will accelerate drug elimination from the body and reduces its half-life of elimination.

- We could also use **ion exchange resins** to enhance drug elimination in case of an overdose; as drugs could be weak acids and bases that bind to these resins thus preventing them from being absorbed.

- Some **cholesterol drugs** are considered ion exchange resins, this could be a problem if a patient take multidrug at a time including one of these cholesterol drugs, as cholesterol resins could bind the other drugs thus decreasing their absorption and lowering their pharmacological effect.

Volume of Distribution (V_D)

- **It is the size of body fluid that would be required if the drug molecules were to be homogeneously distributed through all parts of the body.**
- **It reflects the apparent space available for the drug in the tissues of distribution.**
- **It does NOT represent a real volume.**

- If we **homogeneously** dissolve a specific dose of a drug in a solvent with an unknown volume, then we take a sample of that solvent to measure the concentration of the drug in that sample, we could measure the volume of that solvent. The same concept applies here as we can measure the drug concentration in plasma after a given dose so we can calculate the volume of distribution.

- We **assume** that the drug is **homogeneously** dissolved in the body, which isn't real as drugs aren't distributed equally between the tissues and the fluid compartments of our body.

- **Volume of distribution** isn't a real volume, as it reflects the free space required for the drug to be homogenously dissolved in to give us the calculated concentration.

- **The drug** must be given intravenously to ensure the right calculations of the volume of distribution.

Volume of Distribution (V_D)

- **In a normal 70 Kg man, the volume of:**

Plasma	= 2.8 L
Blood	= 5.6 L
ECF	= 14 L
TBW	= 42 L
Fat	= 14 - 25 L

- **But the volume of distribution for:**

Aminoglycosides	= 5 L
Aspirin	= 11 L
Ampicillin	= 20 L
Phenobarbital	= 40 L
Digoxin	= 640 L
Imipramine	= 1600 L
Chloroquine	= 13000 L

A trend that we can assume:

- When V_D is low, it is more likely that the volume is real, and the drug is really distributed in a volume ≈ V_D
- When V_D is high, the V_D is apparent and caused by low plasma concentration due to many factors (see next slides)

- **Notice the different volumes of distribution** between different drugs, drugs with a very high V_D are less likely to be found in the plasma and are extremely distributed into different tissues (some drugs are even bound to the retina of the eye or to the skin that's why some drugs cause discoloration of the skin such as amiodarone) That's why their apparent volume of distribution are very high.

- **High V_D** indicates that a drug has high lipophilicity or high affinity for binding to tissue proteins.

- **Low V_D** indicates that the drug is either ionized (hydrophilic) or has high affinity to plasma proteins.

- **Digoxin** has a high V_D, because it has high affinity for binding with skeletal and cardiac muscle tissues. This is also a reason why it has a long half-life of a week.

- **Aminoglycosides** has a low V_D of 5L, as these antibiotics are concentrated in the blood because they are ionized and can't easily cross the vessels into other compartments. They are given by IM injections and are eliminated by the kidneys.

- **Imipramine**: part of it is bound to tissues, the rest is either bound to the plasma proteins or circulate freely in the blood; that's why the free dose is very low since it binds to both tissues and plasma proteins.

According to this resource click here, amikacin, which is an aminoglycoside has a V_D of approximately 17.5L for a 70kg person

According to different resources, digoxin half-life ranges from 36 to 48 hours, click here.

Volume of Distribution (V_D)

- The apparent volume of distribution will be small if the drug is restricted to plasma:

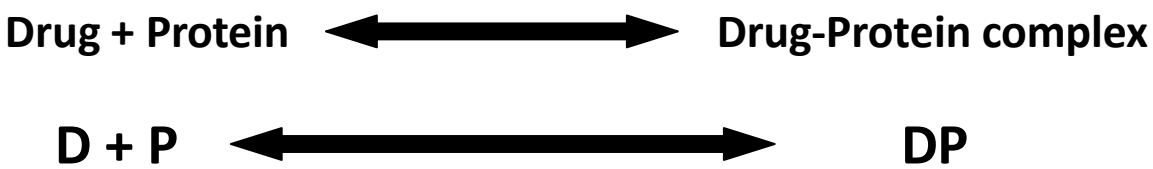
1. due to binding to plasma proteins
2. when it is highly ionized at plasma pH.

- **The apparent volume of distribution will be large when the drug distributes into tissues.**
- **It relates the amount of the drug in the body (Ab), with its plasma concentration (Cp), such that: $V_D = Ab/Cp$**

  - Ab: amount of the drug in the body (IV injected dose).
  - Cp: drug concentration in the plasma.

Drug Binding in Plasma

- **Albumin is the most important drug- binding protein.**
- **α_1- Acid-glycoprotein is also important for binding certain basic drugs.**
- **Binding to plasma proteins is mostly reversible.**



- **Albumin** could bind both acidic and basic drugs.
- **α_1- Acid-glycoprotein** is an acute phase protein, its levels increase in certain diseases.
- There could be an **irreversible covalent interactions** of some drugs with plasma proteins, but most of the times the (drug – plasma proteins) interactions are reversible and in a state of equilibrium.
- If the **free drug concentration** (D) becomes low, the equilibrium will shift to the left, thus drug-protein complex is considered as a reservoir of the drug.
- If **two drugs that binds to albumin** are taken together, they will compete in binding to albumin, this will displace the drug with the lower affinity to albumin leading to increased concentration of that drug which may lead to toxicity (higher plasma concentration than usual for a given dose).

Drug Binding in Plasma

- **The free unbound drug fraction (D) is responsible for the pharmacological action and is also available for elimination.**
- **The bound drug fraction (DP) is not so available, and it represents a reservoir for the drug.**
- **One clinical importance of plasma protein binding of drugs is to help interpretation of measured plasma drug concentration of such drugs.**

Drug Binding in Plasma

- **When plasma protein concentrations are lower than normal, then the total drug concentration will be lower than expected, but the free concentration may not be affected (why?).**
- **Plasma protein binding is also a site for drug-drug interactions.**
- **If a drug is displaced from plasma proteins it would increase the unbound drug concentration and increase the drug effect and, perhaps, produce toxicity.**

Drug Binding in Plasma

- **Drug displaced from plasma protein will of course distribute throughout the volume of distribution, and its rate of elimination will also increase, thus, its plasma concentration will NOT increase dramatically.**

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	**Added Slide 2 (Quiz)**		
	Plasma Concentration vs Time (Part 3)	The integrand is [C(t)]dt	The integrand is [C(t) - MEC]dt
	Plasma Concentration vs Time (Part 4)	Rate is C_{peak}/t_{peak}	Rate is $1/t_{peak}$ changes made accordingly on the graph and texts
V1 → V2	7	$For\ Drug\ 2 \rightarrow \frac{\Delta C}{t_{peak}} = \frac{1}{t_2}$ $For\ Drug\ 3 \rightarrow \frac{\Delta C}{t_{peak}} = \frac{1}{t_3}$	$For\ Drug\ 2 \rightarrow \frac{1}{t_{peak}} = \frac{1}{t_2}$ $For\ Drug\ 3 \rightarrow \frac{1}{t_{peak}} = \frac{1}{t_3}$

Additional Resources:

رسالة من الفريق العلمي:

Lippincott Illustrated Reviews Pharmacology
7th edition, chapter 1, V. Drug Distribution.

Katzung Basic and Clinical Pharmacology,
12th ed., chapter 3.

اللهم إنا نستودعك غزة وأهلها، اللهم انصرهم وثبت اقدامهم، اللهم كن لهم ناصرًا ومعينًا.

﴿ وَنُنَزِّلُ مِنَ ٱلْقُرْءَانِ مَا هُوَ شِفَآءٌ وَرَحْمَةٌ لِّلْمُؤْمِنِينَ ۙ وَلَا يَزِيدُ ٱلظَّٰلِمِينَ إِلَّا خَسَارًا ﴿٨٢﴾ ﴾