Oral administration
part III

PK theory lec.11

Determination of the Model Parameters

[ثابته بما انه فش تغير ع حاله اما يزيد فهي ثابته] *

- K
- Elimination half life
- Ka
- Absorption half life
- t_{max} and C_{max}
- Clearance
- Volume of distribution
- AUC

Determination of the Model Parameters

- Elimination half life = 0.693/K
- Absorption half life = 0.693/Ka
- t_{max} (or t_p):

$$t_{max} = \frac{2.303}{(Ka - K)} \log \frac{Ka}{K}$$

$$t_{max} = \frac{\ln(Ka / K)}{(Ka - K)}$$

- C_{max} (Conc at t = t_{max})

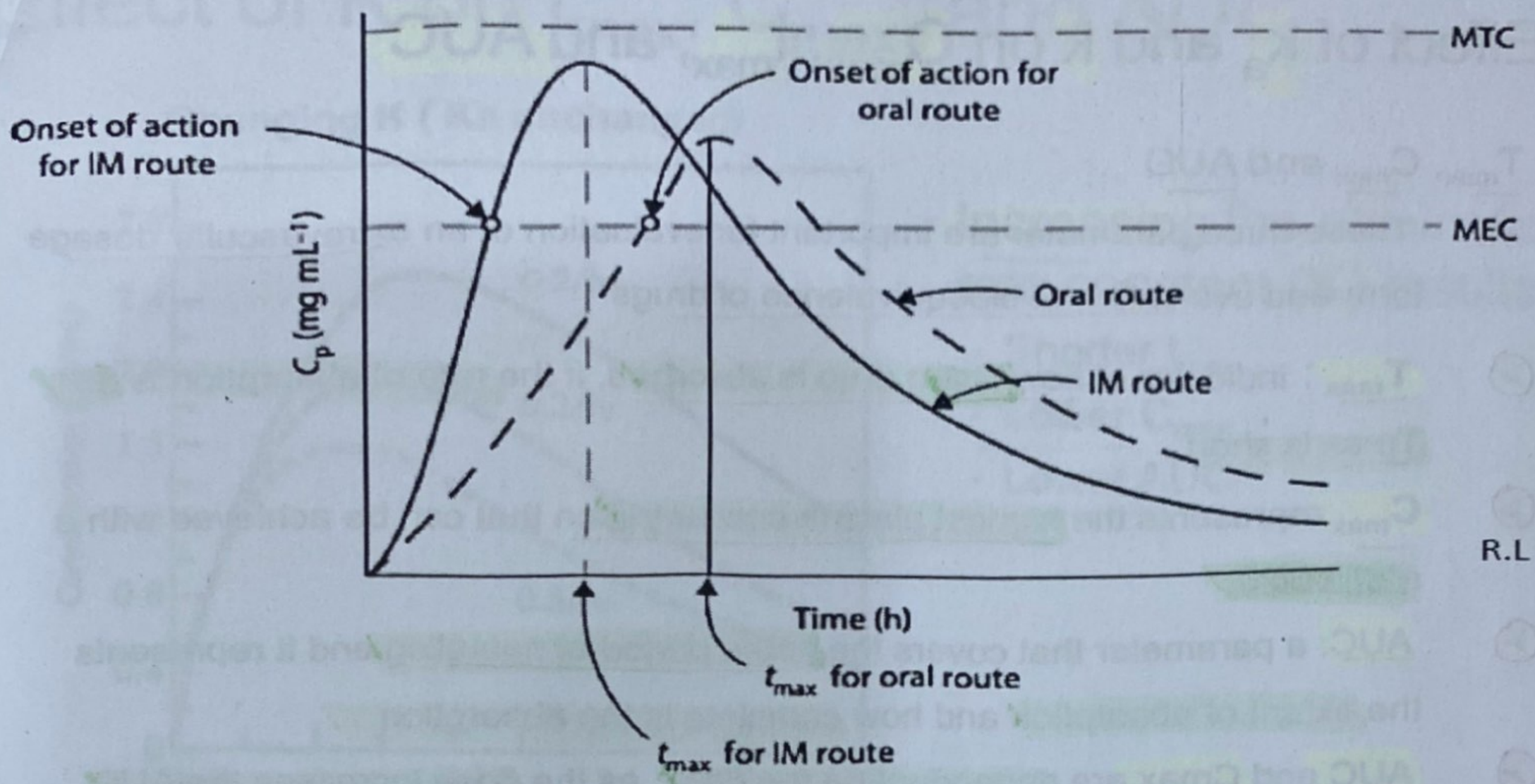
$$C_{max} = \frac{KaFXo}{Vd(Ka - K)} \left[e^{-Kt_{max}} - e^{-Kat_{max}} \right]$$

* ما تخربطوا بقوانين log و ln
* وما تنسوا دخلوا الاقواس بالآلة الحاسبة

Maximum (peak) plasma concentration $(Cp)_{max}$

The peak plasma concentration (Cp_{max}) occurs when time is equal to t_{max}

1. Cp_{max} can be determined from the graph of plasma concentration vs. time



For an identical dose of drug for oral and IM route of administration

Determination of the Model Parameters

نفس كانون الي قبل بس هون حنفنا الـ (f)

$$Cl = \frac{FXo}{AUC}$$

$$Vd = \frac{FXo}{K.AUC}$$

$$AUC = \frac{KaFXo}{Vd(Ka-K)}\left[\frac{1}{K} - \frac{1}{Ka}\right]$$

$$AUC = \frac{FXo}{KVd}$$

* في Parameters ما بتغير شو ما عملت.

- لو نفس الدواء غيرت [dosage form] أو [route of adminstration]

↓ رح يعطي

كل Parameter نفس شي

المعني same

① clearence
② Vd
③ K
④ t half life.
t½ elim.

* الاشي الوحيد الي بتغير شو هو؟؟

* عندي (Ka) ثابت لنفس الدواء اذا اعطيته بنفس

dosage form
formulation
route of adminstration

لو غير أي وحدة منهم بتغير Ka

* إذا أعطيتهم ب [different]

dosage form
formulation
route. of adminstration

أنا بعرف لو غيرت Ka بتغير tmax / Cmax

ما بتغير AUC

محاضرة (1)

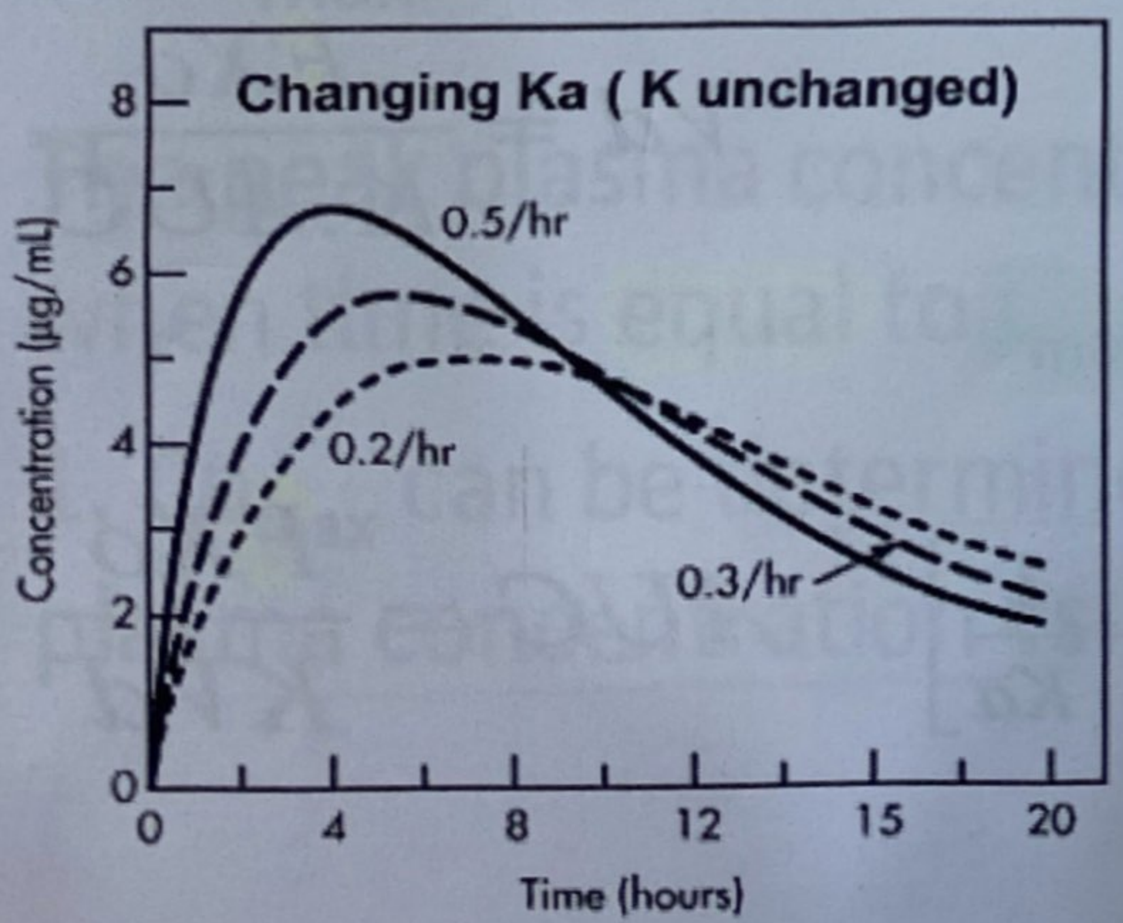
Effect of k_a and k on C_{max}, t_{max}, and AUC

T_{max}, C_{max} and AUC

- These three parameter are important for evaluation of an extravascular dosage form and evaluation of bioequivalence of drugs
- **T_{max}**: indicator of how fast a drug is absorbed, if the rate of absorption is fast, Tmax is short
- **C_{max}** represents the highest plasma concentration that can be achieved with a single dose
- AUC: a parameter that covers the entire period of sampling and it represents the extent of absorption and how complete is the absorption
- AUC and Cmax are dependent on the dose, as the dose increases the AUC and Cmax increase

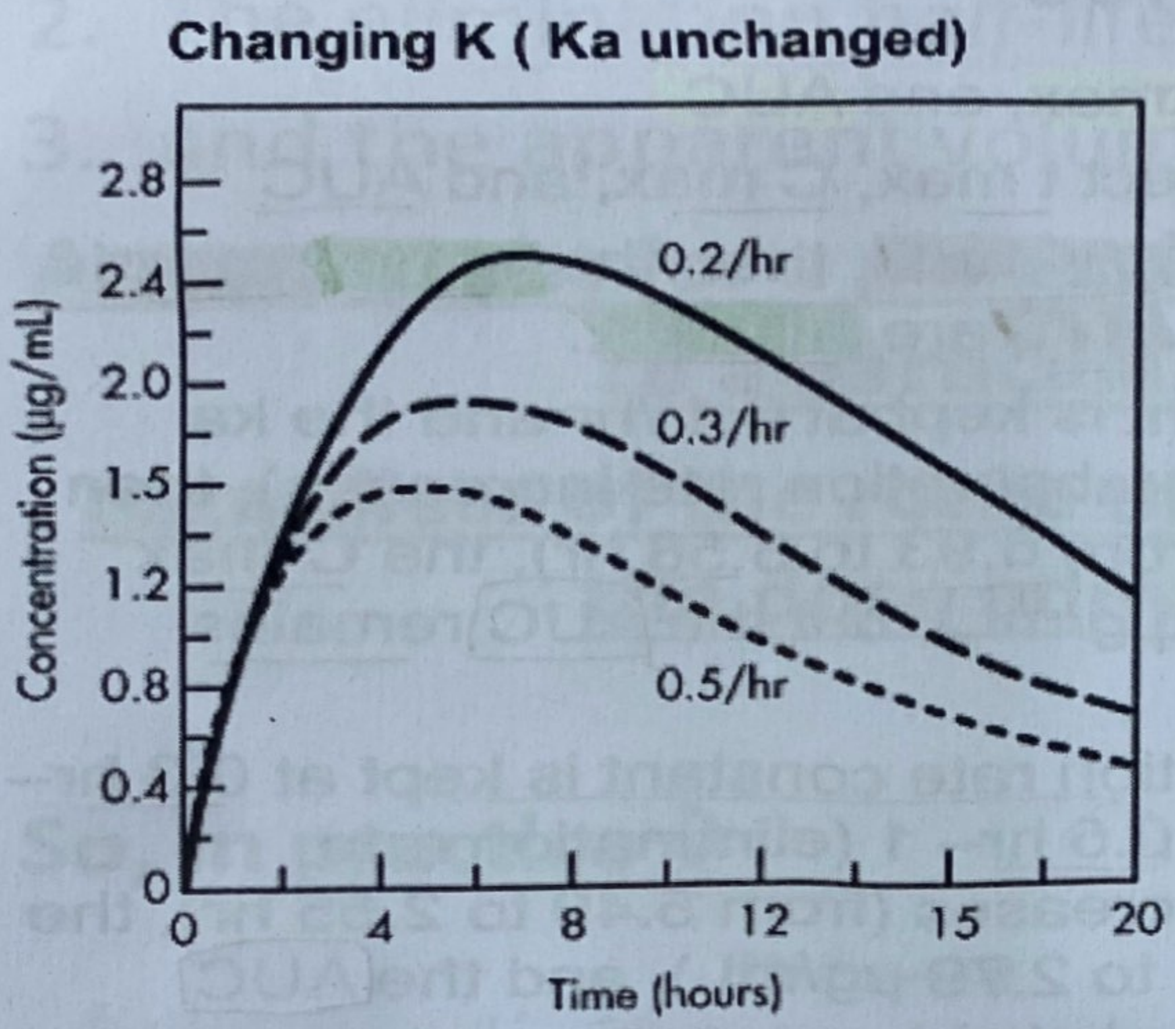
AUC :- * مقدار تعرض الجسم لجرعة معينه من الدواء

Effect of Ka on t_{max}, C_{max}, and AUC



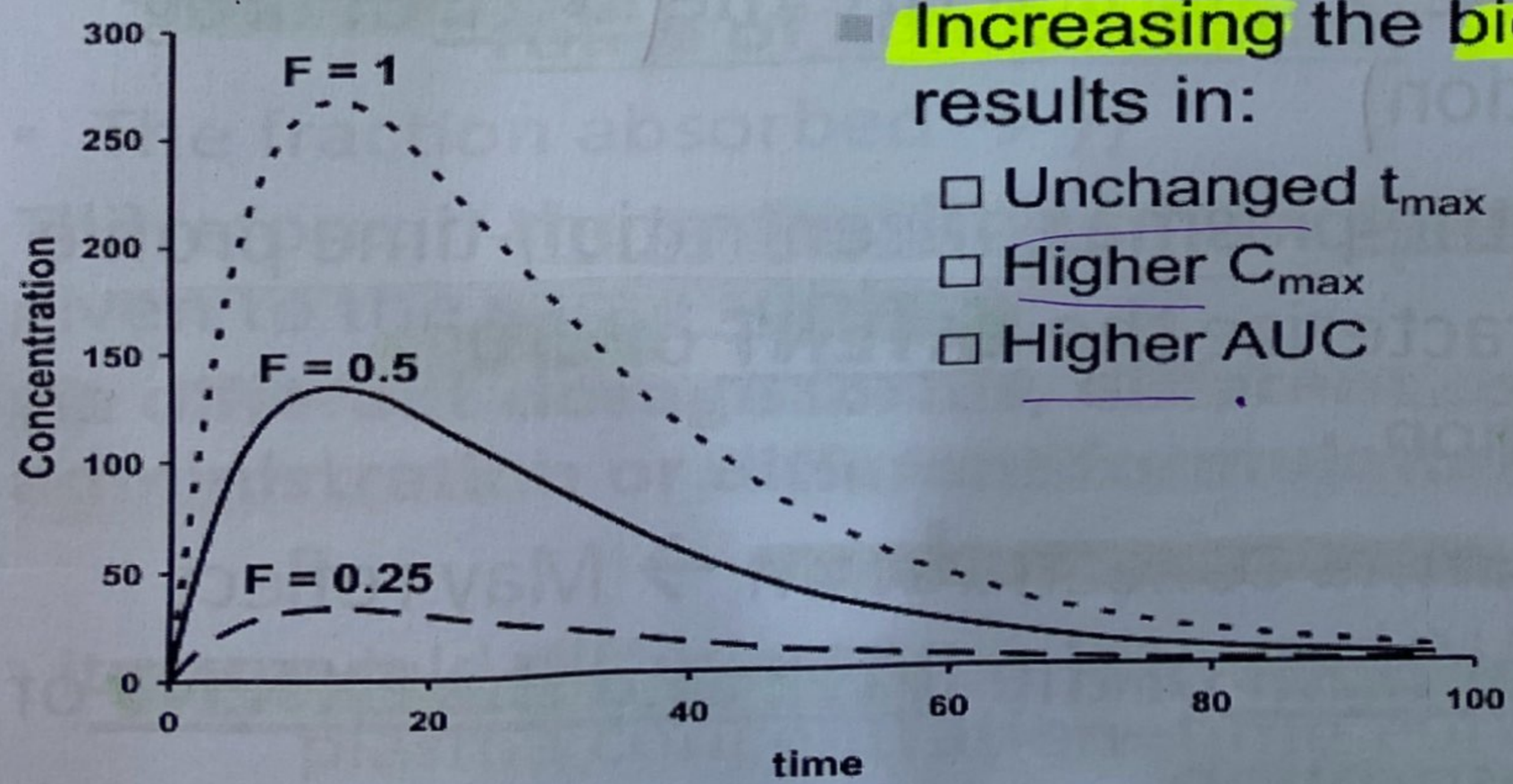
- Increasing the absorption rate constant (Ka) results in:
  - Shorter t_{max}
  - Higher C_{max}
  - Unchanged AUC

Effect of K on t_{max}, C_{max}, and AUC



- Increasing the elimination rate constant (K) results in:
  - Shorter t_{max}
  - Lower C_{max}
  - Lower AUC

Effect F on t_{max}, C_{max}, and AUC



- Increasing the bioavailability results in:
  - Unchanged t_{max}
  - Higher C_{max}
  - Higher AUC

Pharmacokinetic parameters of oral absorption-examples

- Effect of ka and k on Cmax, tmax, and AUC
- Changes in ka and k may affect t max, C max, and AUC
- If the values for ka and k are reversed, then the same t max is obtained, but the C max and AUC are different.
- If the elimination rate constant is kept at 0.1 /hr and the ka changes from 0.2 to 0.6 hr^{-1} (absorption rate increases), then the tmax becomes shorter (from 6.93 to 3.58 hr), the C max increases (from 5.00 to 6.99 µg/mL), but the AUC remains constant (100 µg hr/mL).
- In contrast, when the absorption rate constant is kept at 0.3 hr– 1 and k changes from 0.1 to 0.5 hr– 1 (elimination rate increases), then the tmax decreases (from 5.49 to 2.55 hr), the C max decreases (from 5.77 to 2.79 µg/mL), and the AUC decreases (from 100 to 20 µg hr/mL).

Notes:

- Peak time → Characterize the **RATE** of drug absorption
- AUC of the plasma concentration-time profile → Characterize the **EXTENT** of drug absorption
- Peak plasma concentration → May reflect **either or both** of the **RATE and the EXTENT** of drug absorption

يعني ماحكينا هدول بكونوا ثابتين :- يعني لو نفس الدواء غيرت الـ dosage form او formulation أو route of adminstration الـ parameter نفس شي.

1. The elimination rate constant (k)
2. The elimination half-life ($t_{0.5(elim)}$)
3. and the apparent volume of distribution (V_D)

Are constant for a particular drug administered to a particular patient regardless of the route of administration (*) and the dose administered (*)

So, in practice→

* في المحاضرة الاسئلة سؤال انه الدواء نعطي IV bolus ونفس الدواء ابكرن اعطاني oral و اعطاني بالسؤال بعض القيم للـ Vd تبع الـ IV bolus ف انا هون باخذ Vd تبع oral عادي صح.

بس اللي تختلف بالقيم هي [Cmax / tmax /AUC] لانه (IV) ما بصير عندها absorption (مباشرة بروح ع (General Circulation)

نفس الحكي الي كتبته بالدفتر.

- The absorption rate constant (ka) is a constant for:

a given drug formulation, dosage form and route of administration

- The fraction absorbed → //

Therefore, if **the same dose** of the **same drug** is given to the **same subject** via **different dosage forms, different routes of administration or different formulations**

↓

it may yield **different t_{max}, C_{max} and AUC** of the plasma concentration–time curve

*** عشان أحسب (F) لازم اعطي الدواء (IV) واحسب Clearance وبعدين

اعطي الدواء (orall) وبعدين هيك: ← عندي dose ✓، عندي CL ✓، عندي AUC ✓ ← بطلع (F).

الـ Bioavailability عبارة عن $\left(F = \frac{AUC_{oral}}{AUC_{IV}}\right)$ بشرط ثبات الـ dose.

same dose: 50 mg oral / 50 mg IV → $\frac{AUC}{AUC}$

different dose: $\frac{AUC}{AUC}$ × مقلوب الـ dose.

Bioavailability

- Systemic absorption is often incomplete when given extravascularly. Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action

- Knowing the extent of absorption (bioavailability) helps to en-sure that the correct dose is given extravascularly to achieve a therapeutic systemic expo-sure

- Although dose is known and area can be determined following an extravascular dose, clearance is needed to estimate bioavailability

Bioavailability

- To determine clearance, a drug must be given intravascularly, as only then is the amount entering the systemic circulation known (the dose, F =1):

$$Dose_{IV} = Cl \cdot AUC_{IV}$$

- After an oral dose:

$$F \cdot Dose_{oral} = Cl \cdot AUC_{oral}$$

- Given that Clearance is unchanged, F is estimated by:

$$F = \frac{AUC_{oral}}{AUC_{IV}} \cdot \frac{Dose_{IV}}{Dose_{oral}}$$

Bioavailability

- If the IV and oral doses were **equal**, F can be calculated according to:

اذا كانت الـ dose متساوية

$$F = \frac{AUC_{oral}}{AUC_{IV}}$$

Example 1

- A 500-mg dose of the sulfonamide sulfamethoxazole is administered as an oral tablet to a human subject. Eighty percent of the drug is absorbed, and the balance is excreted unchanged in feces. The drug distributes into an apparently homogeneous body volume of 12 L, and has an absorption half-life of 15 hr and overall elimination half-life of 12 h.

من السؤال

- $X_0 = 500\ mg$
- $F = 0.8$
- $V_d = 12\ l$
- absorption half life = 15 hr
- elimination half life = 12 hr

1) Calculate the following:
(i) AUC0→∞, (ii) tmax and (iii) C max.
① ② ③

2) Recalculate the values in Problem 1 if all parameter values remained unchanged, but the elimination half-life was increased to 18 h.

شو راح يصير؟

① Shorter t_{max}
② lower C_{max}
③ lower AUC

Example 1

- Estimate k and ka:

$$k_a = 0.693/t_{1/2}^{abs} = 0.693/15 = 0.046\ hr^{-1}$$

$$k = 0.693/t_{1/2}^{elimin} = 0.693/12 = 0.058\ hr^{-1}$$

- Estimate AUC:

$$AUC = \frac{FXo}{KVd} = \frac{0.8 * 500}{0.058*12} = 575\ mg \cdot hr/L$$

Example 1

- Estimate t_{max}:

$$t_{\max} = \frac{2.303}{(Ka - K)} \log \frac{Ka}{K}$$

$$= \frac{2.303}{(0.046 - 0.058)} \log \frac{0.046}{0.058} = 19.32\ hr$$

Example 1

- Estimate C_{max}:

$$C_{max} = \frac{KaFXo}{Vd(Ka-K)}\left[e^{-Kt\,max} - e^{-Kat\,max}\right]$$

$$C_{max} = \frac{0.046*0.8*500}{12(0.046-0.058)}\left[e^{-0.058*19.32} - e^{-0.046*19.32}\right]$$

$$C_{max} = 10.9\ mg/L$$

Example 1

Recalculate the values in Problem 1 if all parameter values remained unchanged, but the elimination half-life was increased to 18 h

$K = \frac{0.693}{18}$

absorption rate constant

$$k = 0.039\ hr^{-1}$$

$$t_{max} = 23.5\ hr$$

$$AUC = 855\ mg \cdot hr/L$$

$$C_{max} = 13.3\ mg/L$$