Pharmacokinetics

2025-2024

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ARKAN ACADEMY

Extravascular Administration

- Q1: 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 min and overall elimination half-life of 12 h.

1) **Calculate the following:**
(i) $AUC_{0\rightarrow\infty}$, (ii) tmax and (iii) C max.

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

$X_o = 500$ mg
$F = 0.8$
$Vd = 12$ L
Abs $t_{0.5} = 15$ min $= 0.25$ hr
$Ka = \frac{0.693}{0.25} = 2.772\ hr^{-1}$
Elm. $t_{0.5} = 12$ hr
$K = \frac{0.693}{12} = 0.0578\ hr^{-1}$

$Ka \gg K$

Normal

① AUC . tmax . Cmax

1- $AUC = \frac{FX_o}{KVd} = \frac{0.8 * 500}{0.0578 * 12}$

$= 577$ mg.hr/L

2- $t_{max} = \frac{\ln\left(\frac{Ka}{K}\right)}{Ka - K} = \frac{\ln\left(\frac{2.772}{0.0578}\right)}{2.772 - 0.0578}$

$= 1.43$ hr

3- $C_{max} = \frac{FX_o}{Vd} e^{-Kt_{max}}$

$= \frac{0.8 * 500}{12} e^{-0.0578 * 1.43}$

$= 30.7$ mg/L

② If Elimination $t_{0.5} = 18$ hr
↳ $K = 0.0385\ hr^{-1}$

1- $AUC = \frac{FX_o}{KVd} = \frac{0.8 * 500}{0.038 * 12}$

$= 865.8$ mg.hr/L

2- $t_{max} = \frac{\ln\left(\frac{2.772}{0.0385}\right)}{2.772 - 0.0385}$

$= 1.57$ hr.

3- $C_{max} = \frac{FX_o}{Vd} e^{-Kt_{max}}$

$= \frac{0.8 * 500}{12} e^{-0.385 * 1.57}$

$= 31.39$ mg/L

- Q2: A patient received a single dose of 500 mg erythromycin in the form of a tablet that is known to have 80% bioavailability. Calculate:

1) **The time to reach the maximum concentration.**
2) **The maximum concentration.**
3) **AUC and Clearance after this single dose If K is 0.2 hr-1, Ka is 1.3 hr-1, and and Vd is 40 liters.**

$X_o = 500\ mg$

$F = 0.8$

$k = 0.2\ hr^{-1}$

$ka = 1.3\ hr^{-1}$

$Vd = 40L$

$Ka > K$

flip-flop.

① $t_{max} = \frac{\ln\left(\frac{ka}{k}\right)}{ka - k}$

$= \frac{\ln\left(\frac{1.3}{0.2}\right)}{1.3 - 0.2}$

$= 1.7\ hr$

② $C_{max} = \frac{FX_o}{Vd} e^{-kt_{max}}$

$= \frac{0.8 * 500}{40} e^{-0.2 * 1.7}$

$= 7.12\ mg/L$

③ $AUC = \frac{FX_o}{KVd}$

$= \frac{0.8 * 500}{0.2 * 40} = 50\ mg \cdot hr/L$

④ $CL = KVd$

$= 0.2 * 40$

$= 8L$

- Q3: The relative bioavailability of a new oral drug product compared to a reference standard preparation is 0.9 and the absolute bioavailability of the reference standard preparation is 0.8. What is the absolute bioavailability of this new oral drug product?

1) 0.8 2) 0.9 3) 0.72 4) 0.85

relative bioavailability = 0.9

New A → absolute BA = ?

Refferance B → absolute BA = 0.8

$$\text{Relative BA} = \frac{\text{absolute A}}{\text{absolute B}}$$

$$0.9 = \frac{\text{absolute A}}{0.8}$$

absolute = 0.72

- Q4: Ciprofloxacin is a quinolone antibiotic used in the treatment of urinary tract infections. After administration of a single iv dose of 5 mg/kg ciprofloxacin the AUC calculated using the trapezoidal rule was 14 mg-hr/L. If the AUC measured after administration of a single oral dose of 10 mg/kg ciprofloxacin to the same individual was 16.8 mg-hr/L, calculate the absolute bioavailability of this oral formulation.

1) 0.95 2) 1.2 3) 0.8 4) 0.6

IV administration

$X_0 = 5\ mg/kg$

$AUC = 14\ mg.hr/L$

Oral administration

$X_0 = 10\ mg/kg$

$AUC = 16.8\ mg.hr/L$

$$F = \frac{AUC_{oral}}{AUC_{IV}} * \frac{X_{oIV}}{X_{oral}}$$

$$= \frac{16.8}{14} * \frac{5}{10}$$

$$= 0.6$$

- Q5) An oral ibuprofen solution was used as the reference standard in the evaluation of the relative bioavailability of a new oral solid dosage form of ibuprofen. Ibuprofen AUC after administration of 200 mg oral solution was 65 mg-hr/L, and after administration of 400 mg of the new product the AUC was 130 mg-hr/L. What is the relative bioavailability of the new ibuprofen product?

1) 1.0 2) 0.5 3) 2.0 4) 0.65

formula ①

$X_0 = 200\ mg$

$AUC = 65\ mg.hr/L$

formula ②

$X_0 = 400\ mg$

$AUC = 130\ mg.hr/L$

$$F = \frac{AUC_2}{AUC_1} * \frac{X_{o1}}{X_{o2}}$$

$$= \frac{130}{65} * \frac{200}{400}$$

$$= 1$$

- Q6) The time to achieve the maximum plasma concentration after oral administration of a drug is dependent on:

  1) The dose and bioavailability
  2) The absorption rate constant only
  3) The elimination rate constant only
  4) Both elimination and absorption rate constants

$$t_{max} = \frac{\ln\left(\frac{ka}{k}\right)}{ka - k}$$

- Q7) The flip flop of k and ka is commonly observed when:

  1) Drug absorption and drug elimination have similar rates
  2) Drug absorption is faster than drug elimination
  3) Drug elimination is faster than drug absorption
  4) Drug elimination is very slow and the half-life is very long

flip-flop $\longrightarrow$ $k >> ka$

- Q8) Procainamide is a class Ia antiarrhythmic drug that alters the conduction in normal and ischemic cardiac tissues by sodium-channel blockade. After administration of a single oral dose of 600 mg procainamide to a patient the observed AUC was 15 mg-hr/L. What is the TBC of procainamide in this patient if the bioavailability of oral procainamide is 88%?

  1) 40 L/hr 2) 35 L/hr 3) 528 L/hr 4) 70 L/hr

$X_0 = 600$ mg.

AUC = 15 mg.hr/L

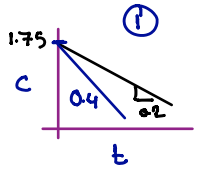
F = 0.88

$$\text{Total body CL} = \frac{F X_0}{AUC}$$

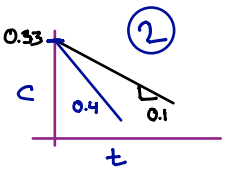
$$= \frac{0.88 \times 600}{15}$$

$$= 35.2 \text{ L/hr}$$

- Q9) A drug company has developed two oral formulations (formulation I and II) of the investigational compound TTK-026. Following administration of 50 mg of each formulation to healthy volunteers, plasma concentrations (in mg/L) were measured and plotted against their corresponding times (in hr), the equations obtained from the plots are presented in the table below



Oral Data	Formulation I	Formulation II
Terminal equation	$C_t=1.75e^{-0.2t}$	$C_t=0.33e^{-0.1t}$
Residual equation	$C_t=1.75e^{-0.4t}$	$C_t=0.33e^{-0.4t}$



When 44 mg of TTK-026 was given IV the following equation was obtained $C_t=2.19^{e-0.4t}$, answer the following:

X_o oral = 50 mg | X_{oIV} = 44 mg.
K = 0.4 hr^{-1} | C_o = 2.19

1.What is the kind of Pharmacokinetics TTK-026 exhibits (Normal or Flip-Flop).

$K >> Ka$

Flip-Flop

2. What is AUC after the IV dose.

$AUC = \frac{C_o}{K}$

$= \frac{2.19}{0.4} = 5.475$ mg.hr/L

$Vd = \frac{X_o}{C_o} = \frac{44}{2.19}$

$= \boxed{20L}$

3. The bioavailable fraction of formulation I is

$F = \frac{AUC_1}{AUC_{IV}} * \frac{X_{oIV}}{X_{o1}}$

$= \frac{4.374}{5.475} * \frac{44}{50} = 0.703$

$AUC_1 = \frac{A}{Ka} - \frac{A}{K}$

$= \frac{1.75}{0.2} - \frac{1.75}{0.4} = 4.374$ mg.hr/L

4. Absorption half life for formulation II in hours is

$Abs.\ t_{0.5} = \frac{0.693}{Ka}$

$= \frac{0.693}{0.1} = 6.93$ hr

5. Cmax for formulation II is (in mg/L)

$t_{max} = \frac{\ln(\frac{0.4}{0.1})}{0.4-0.1}$

$= 4.63$ hr

$AUC = \frac{A}{Ka} - \frac{A}{K}$

$= \frac{0.33}{0.1} - \frac{0.33}{0.4}$

$= 2.475$ mg.hr/L

$F = \frac{AUC_2}{AUC_{IV}} * \frac{X_{oIV}}{X_{o\ oral}}$

$= \frac{2.475}{5.475} * \frac{44}{50}$

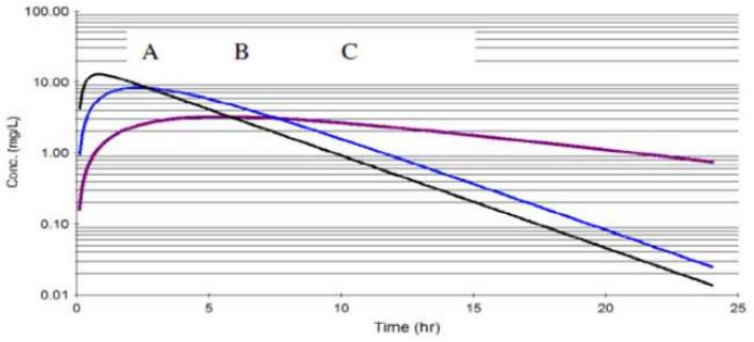
$= 0.4$

$C_{max} = \frac{F X_o}{Vd} e^{-K t_{max}}$

$= \frac{0.4*50}{20} e^{-0.4*4.63}$

$= 0.16$ mg/L

- Q10) The adminstration of a 1000-mg doses of 3 different formulations of Drug-Z resulted in the plasma concentration data presented below.



- The following statement is NOT correct regarding PK of the drug after the 3 formulations

A. C has flip-flop kinetics
B. Ka for A > Ka for B
C. The three formulations have similar absorption half-lives
D. The three formulations have similar elimination half-lives
E. A and B have similar terminal half-lives

- Formulation..... has fastest onset of action

A. A
B. B
C. C
D. A & B
E. B & C

- Q11) Pharmacokinetics of TQ-16 after administration of an oral dose of 400 mg were compared to those obtained after an intravenous dose of 300 mg. The following table summarizes the results of the study

$X_o = 400$ mg (oral)

$X_o = 300$ mg (IV)

Parameter	IV bolus	Oral dose
Cmax (µg/ml)		
AUC∞ (µg.hr/ml)	200	160
Residual half-life(hr)		2
Terminal half-life (hr)	2	6
Xu^{∞} (mg)	120	

flip-flop

$K = \frac{0.693}{2} = 0.3465\ hr^{-1}$

1) The Bioavailability of the drug is:

$$F = \frac{AUC_{oral}}{AUC_{IV}} * \frac{X_{oIV}}{X_{ooral}}$$

$$= \frac{160}{200} * \frac{300}{400} = 0.6$$

2) Renal elimination rate constant is equal to:

$$\frac{Kr}{K} = \frac{X_u^{\infty}}{X_o}$$

$$= \frac{120}{300} * 0.3465 = 0.1386\ hr^{-1}$$

3) The absorption half-life is equal to:

$t_{os} = 6\ hr$

4) The maximum concentration after the IV dose is:

$$C_o = AUC * K$$
$$= 200 * 0.3465$$
$$= 69.3\ mg/L$$

5) The amount of the drug that is expected to be excreted unchanged in urine after the oral dose is:

$$\frac{X_u^\infty}{F X_o} = \frac{K_r}{K}$$

$$X_u^\infty = \frac{0.1386}{0.3465} * 0.6 * 400$$

$$= 96\ mg.$$

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