Pharmacokinetics

2025-2024

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ACADEMY

Area Under the Conc. Time Curve (AUC)

- The best measure for bioavailability (to measure the extent of absorption), could be:
  - **Model dependent:** involves equation/model
    - ✓ We use integration to calculate AUC. لأنه تكامل المنحنى يعني حساب المساحة تحته.

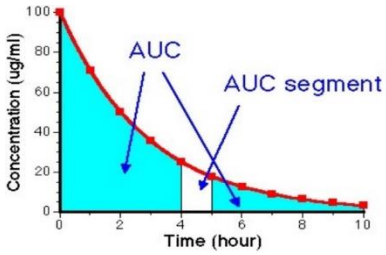
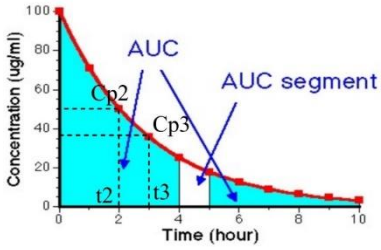
$$\textbf{AUC} = \frac{Xo}{K.Vd} = \frac{Xo}{Cl} = \frac{Co}{K}$$

Unit: Concentration.time (mg.hr/L)

  - **Model-independent (trapezoidal rule):** no equation / we use numerical integration
    - ✓ Numerical integration: we divide the area into small sections and calculate their area.
    - ✓ When we divide the AUC (Area Under the Curve) into several sections, each section will resemble the shape of a trapezoid. The area of a trapezoid is calculated using the formula:

Area of trapezoid: $\frac{(Base1+Base2)}{2} * Height$

    - ✓ This formula helps in calculating the AUC by summing up the areas of these trapezoidal sections.

Model dependent	Model-independent
 $Cp = Co\ e^{-Kt}$ $AUC = \int_0^\infty Cp.dt$ $= \int_0^\infty Co\ e^{-Kt}.dt$ (Co is constant) $= \frac{Co\ e^{-Kt}}{-K} \Big\|_0^\infty \rightarrow \frac{Co}{-K}$ (0 – 1) $AUC = \frac{Co}{K}$ $AUC = \frac{Xo}{K.Vd} = \frac{Xo}{Cl} = \frac{Co}{K}$	 $AUC = \frac{(Cp3+Cp2)}{2} * (t3 - t2)$ This way, we keep summing the AUC for each segment until we reach the last concentration, Clast. Note: The initial concentration, Co, isn't directly available, so I need to extend a line (extrapolation) to see where it intersects the y-axis. As for the last concentration, Clast, I can't directly calculate it without integration, similar to the first method: $AUC = \frac{Clast}{K}$ Where k is the elimination rate constant.

- ***Note:***
  - e^{-Kt} : decay function.
  - $-e^{-Kt}$: growth function.

Clearance (CL)

- **Definition:** is the ratio of the rate of elimination by all routes to the concentration of the drug in plasma.

  - $CL = \frac{\text{Rate of elimination } \left(\frac{mg}{h}\right)}{\text{C in plasma } \left(\frac{mg}{L}\right)}$

  - **Unit:** Volume/Time (L/h) or adjusted for body weight (l/h/kg)

$$\boldsymbol{Cl = K\ Vd}$$

- ***Notes:***
  - There is no need for a negative sign (-) because it's a measurement of elimination (we already know it's a loss process).
  - The volume of serum or blood completely cleared of the drug per unit of time.
  - It measures the **elimination efficiency** of all elimination organs (liver, kidney, gastrointestinal wall, lung, bile…) thus It's an additive parameter:
    $Cl_{total} = Cl_{RENAL} + Cl_{HEPATIC} + Cl_{PULMONARY} + \ldots\ldots$
    NOTE: usually we divide clearance into renal and non-renal

  - Clearance (Cl) is the most important pharmacokinetic parameter because it determines the maintenance dose (**MD**) that is required to obtain a given steady-state serum concentration (Css): MD = Css
  - Clearance itself is a **model-independent parameter** (we don't need to know the number of compartments to calculate clearance whether we calculated it through a dependent or independent way we will end with the same value).
  - So, the Clearance: the **volume of serum or blood** completely **cleared** from the drug **per unit time**.
  - The liver is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug excretion.
  - The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile.

- **Model dependent:** **Clearance = (dC/dt) /Cplasma** or **Clearance = K*Vd**
  note: both rate and conc. in plasma are at the same time .

- **Model-independent (trapezoidal):**
  Using integration: **Clearance = Xo / AUC**

Cl total = Cl renal + Cl non-renal
K*Vd = (Kr *Vd) + (Knr* Vd)
= Vd (Kr + Knr)
= Vd K

Kr: K for renal
Knr: K for non-renal

- **Questions:**
  - The units for clearance are:
    A) Concentration/half-life
    B) Dose/volume
    C) Half-life/dose
    D) Volume/time

    Answer: D) Volume/time

  - Total body clearance is the sum of clearance by the kidneys, liver, and other routes of elimination.
    A) True
    B) False

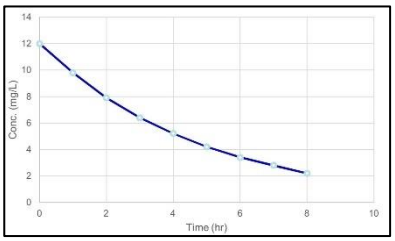
    Answer: A) True.

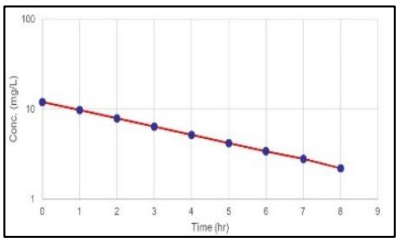
  - To determine drug clearance, we must first determine whether a drug best fits a one- or two-compartment model.
    A) True
    C) False

    Answer: B) False, because clearance Is a model-independent parameter

  - Drug Y is given by an intravenous injection and plasma concentration are then determined as follows:

Time after injection (hr)	Conc (mg/L)
0	12
1	9.8
2	7.9
3	6.4
4	5.2
5	4.2
6	3.4
7	2.8
8	2.2





    Is the drug eliminated by a first or zero order process? Defined your answer
    Answer: We can plot time and conc. on both NORMAL and SEMI-LOG paper and examine:
    If we get linearity on normal paper : zero order.
    If we get linearity on semi-log paper: first order
    But what if we don't have semi-log or normal paper? Simply, we know that the rate of reaction in first-order rxns changes as the concentration changes So the rate is decreasing (changing): first-order reaction

  - Which of the following patient scenarios is associated with a smaller volume of distribution?
    A) Dose = 500 mg and initial serum concentration = 40 mg/L
    B) Dose = 20 mg and initial serum concentration = 1.5 mg/L

    Answer: Vd=Xo/Co

    A → Vd=500/40=12.5 L
    B → Vd=20/1.5=13.3 L
    A is smaller volume of distribution.

- Explain how a person who weighs 70 kg can have a volume of distribution for a drug 700 L.
  Answer: Vd is apparent not physiological value so it can be larger than body volume (it describes the affinity of the drug)

- For drug X, individual organ clearance have been determined as follows:

Renal clearance	180 mL/minute
Hepatic clearance	22 mL/minute
Pulmonary clearance	5.2 mL/minute

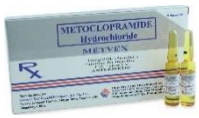
How would you describe the clearance of drug X?

Answer: Drug X is eliminated by three systems (renal, hepatic, and pulmonary), total CL=207.2mL/min but it's mainly eliminated by the renal system.

Cases in IV Bolus

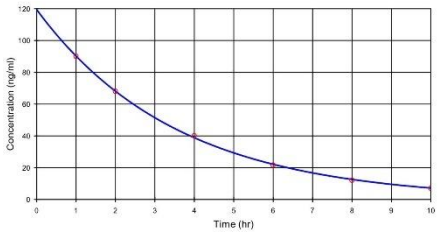
- **Case 1:** Ten mg metoclopramide were administered intravenously to a 72 kg patient. The minimum plasma concentration required to cause significant enhancement of gastric emptying is 50ng/mL. The following plasma concentrations were observed after analysis of the specimen.

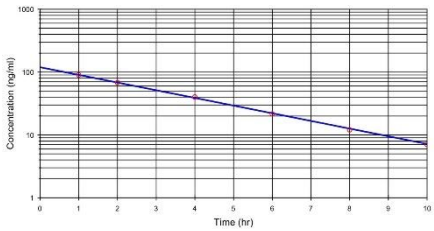
Time (hr)	Cp (ng/mL)
1	90
2	68
4	40
6	21.5
8	12
10	7



*Before starting the solution, let's summarize the information we have from the question:
Dose (Xo) = 10 mg
Minimum effective concentration = 50 ng/ml ~ 50 mcg/L ~ 0.05 mg/L

- **Plot the metoclopramide concentration-time data and draw a compartmental scheme showing the number of compartment involved.**





- **Write the equation describing the disposition kinetics of the drug. ($Ct = Co\ e^{-Kt}$)**
  - ✓ From the plot extrapolation Co = 120 ng/ml ~ 120 mcg/L ~ 0.120 mg/L.
  - ✓ $-K = \text{slope} = \frac{\ln(90) - \ln(40)}{1-4} = -0.28\ hr^{-1}$
  - ✓ **$Ct = 120\ e^{-0.28t}$**

- **Calculate the biological half-life of the drug elimination (t½), the overall elimination rate-constant (K), the volume (Vd), the coefficient of distribution and the duration of action (td).**

1) $t_{0.5} = \frac{0.693}{K} = \frac{0.693}{0.28} = 2.48$ hr
2) K = 0.28 hr^{-1}
3) Vd = $\frac{Xo}{Co} = \frac{10\ mg}{0.12\ mg/L} = 83.3$ L
4) Distribution coefficient = $\frac{83.3\ L}{72\ kg} = 1.157$ L/Kg
5) Duration of action = Ct = Co e^{-Kt}

   50 = 120 $e^{-0.28 * td}$

   td = 3.13 hr
6) AUC = $\frac{Co}{K} = \frac{120\ ng/mL}{0.28\ hr^{-1}} = 425$ ng.hr/Ml
7) Cl = K Vd = 0.28 hr^{-1} * 83.3 L = 23.5 L/hr

- **Comment on the extent of metoclopramide distribution in the body.**

  The patient weight 72, and the Vd= 83 (the volume of distribution is higher than the patient weight) , it indicates that the drug has a strong affinity for tissues. The drug tends to distribute and accumulate in body tissues rather than staying primarily in the blood.

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- **Case 2:** An adult male patient was given the first dose of an antibiotic at 6:00 AM. At 12:00 noon the plasma level of the drug was measured and reported as 5 µg/ml. The drug is known to follow the one-compartment model with a half-life of 6 hours. The recommended dosage regimen of this drug is 250 mg q.i.d. the minimum inhibitory concentration is 3 µg/ml. Calculate the following:

*Before starting the solution, let's summarize the information we have from the question:

Xo = 250 mg Xo = 250 mg Ct = 5 mg/L

$t_{0.5}$ = 6 hr → K = 0.1155 hr^{-1}

minimum effective conc = 3 µg/ml ~ 3 mg/L

- **The apparent volume of distribution**

Solution 1: Vd = $\frac{Xo}{Co}$

Since the half-life is 6 hours, and the concentration at 12 pm was 5 mg/L, the concentration 6 hours earlier would have been double that,**10 mg/L**. This corresponds exactly to when we administered the first dose at 6 am.

Vd = $\frac{250\ mg}{10\ mg/L} = 25$ L.

Solution 2: find Co from the given data.

C = **Co** e^{-Kt}

5 = Co $e^{-0.1155*6}$ → Co = 10 mg/L

Vd = $\frac{250\ mg}{10\ mg/L} = 25$ L

- **Expected plasma concentration at 10 AM.**

  At 10 AM -> **4** hours later

  Ct =Co e^{-Kt}

  Ct =10 $e^{-0.1155*4}$

  Ct = 6.3 mg/L

- **Duration of action of the first dose**

  C = 10 e^{-Kt}

  3 = 10 $e^{-0.1155*td}$

  td=10.4 hr

- **Total body clearance**

  Cl = K Vd

  Cl = 0.1155*25

  Cl = 2.89 L/hr

- **Fraction of the dose in the body 5 hours after the injection**

  X=Xo e^{-Kt}

  $\frac{X}{Xo}$ = $e^{-0.1155*5}$ → $\frac{X}{Xo}$= = 0.56

- **Total amount in the body 5 hours after the injection**

  X=Xo e^{-Kt}

  X=250 $e^{-0.1155*5}$

  X=140 mg

- **Exponential and logarithmic equation (pharmacokinetic model)**

  C = 10 $e^{-0.1155*t}$

  LnC = 2.303 - 0.1155t

  LogC = 1 - 0.0502 t

- **Total amount in the body immediately after injection of a second dose at 12:00 noon**

  At 12 noon the first $t_{0.5}$ has reached so → the first dose 250/2 = 125mg + we give a new dose 250mg

  X = 125mg + 250mg

  X = 375 mg

- **Duration of action of first dose only if dose administered at 6:00 AM was 500 mg.**

  Solution 1: C= $\frac{Xo}{Vd}$ = $\frac{500\ mg}{25\ L}$ = 20 mg/L

  3=20*$e^{-0.1155*td}$

  td = 16.4 hr

  Solution 2: The difference between 500 and 250 represents one half-life. Therefore, doubling the dose in the case of first-order kinetics extends the duration of action by one half-life.

  The duration of action for 250 mg dose = 10.4 hr and the $t_{0.5}$ = 6 hr

  td = 10.4 + 6

  td = 16.4 hr

- **Case 3:** A general anesthetic has a volume of distribution of 15L and a minimum effective concentration of 2µg/mL (the drug is effective as long as the drug concentration is above 2µg/mL). After administration of 120mg of the drug as an IV bolus dose to a patient the drug produced an anesthetic effect for 6 h.

*Before starting the solution, let's summarize the information we have from the question:

Vd = 15 L	Co = Xo/Vd	$C = Co\ e^{-Kt}$
MEC = 2 mg/L	= 120/15	$2 = 8\ e^{-6K}$
Xo = 120 mg	= 8 mg/L	K = 0.23 hr
dt = 6 hr		

$$Ct = 8\ e^{-0.23t}$$

- **Calculate the half-life of this drug.**

Solution 1: $t_{0.5} = \frac{0.693}{K}$

$= \frac{0.693}{0.23} \rightarrow t_{0.5} = 3$ hr

Solution 2: The initial concentration (C_0) is 8. After one half-life ($t_{0.5}$), the concentration drops to 4, and after the second half-life, it drops to 2. After that, the drug no longer has an effect because the concentration falls below the MEC. Therefore, the drug remained effective for two half-lives.

The question mentions that the drug was active for 6 hours. Since it went through two half-lives in those 6 hours, we calculate: 6 hours / 2 half-lives = 3 hours per half-life.

So, the half-life is 3 hours.

- **Calculate the minimum effective concentration for the drug if the dose was 400mg.**
The Minimum Effective Concentration is Constant for any drug and not affected by the dose.

- **Calculate the expected duration of effect if an IV bolus dose of 240mg was administered.**
Solution 1:

$X = Xo\ e^{-0.23t}$

$240 = 120\ e^{-0.23*td} \rightarrow td = 9$ hr

Solution 2: Doubling the dose will increase the duration of action by ONE $t_{0.5}$, The previous duration of action was six hours and the $t_{0.5}$ was 3 hours if we double the dose the duration of action will be:
6+3 = 9 hr

- **Calculate the lowest dose that will produce an effect for 3 h.**
Solution 1:

Xt$= 120\ e^{-0.23t}$

$Xt = 120\ e^{-0.23*3}$

Xt = 60 mg

Solution 2: 3 hrs is $t_{0.5}$ that we calculated before, the first dose was 120, after one $t_{0.5}$ it is : 60 mg

- **Calculate the expected duration of effect if 20mg was given as an IV bolus dose.**
If 20 mg were given, the conc. = 20mg/ 15L= 1.33 is below MEC !!!
So duration of action is Zero.

- **Case 4:** The therapeutic range of a drug is 20-200 mg/L. After an intravenous bolus injection of 1.0 gm followed by regression analysis of the concentration of the drug in plasma (in units of mg/L) versus time (in hours), the following linear equation was obtained:

$$\textbf{\textit{Log Cp}} = 2 - 0.1t$$

*Before starting the solution, let's summarize the information we have from the question:

MEC = 20 mg/L

Xo = 1000 mg

Log Co = 2

Co = 100 mg

$Vd = \frac{Xo}{Co}$

$Vd = \frac{1000}{100}$

Vd = 10 L

$\frac{K}{2.303} = 0.1$

K = 0.2303 hr^{-1}

$t_{0.5}$ = 3 hr

➢ **Duration of action**

$20 = 100\ e^{-0.2303\textbf{td}}$

t = 7 hr.

➢ **Total body clearance**

Cl = K Vd

Cl = 0.2303*10

Cl = 2.303 L/hr

➢ **Rate of elimination at 2 hours**

To find the rate of elimination (**dX/dt** = KX), you first need to determine the amount of the drug remaining at 2-hour.

$X = Xo\ e^{-Kt}$

$X = 1000\ e^{-0.2303*2}$

X = 630.9 mg

$\frac{dX}{dt}$ = KX

= 0.2303*630.9

= 145.3 mg/hr

……..……..

- **Case 5:** Drug X has a therapeutic range of 15-80 mg/L. After an intravenous bolus injection of 500 mg of drug X, the concentration of the drug in plasma (in units of µg/ml) versus time (in hours), were described by the following equation:

$$\textbf{Ct} = 50\ e^{-0.12t}$$

*Before starting the solution, let's summarize the information we have from the question:

MEC = 15 mg/L

Xo = 500 mg

Co = 50 mg/L

Vd = 10 L

K = 0.12 hr^{-1}

➢ **Duration of action after the 500-mg dose.**

$15 = 50\ e^{-0.12*\textbf{td}}$

t = 10 hr

- **Amount eliminated at 2 hours**
  X = 500 e -0.12*2
  X = 393.3 (remains)

  Eliminated = Total - Remain
  = 500 - 393.3
  Eliminated = 106.7 mg

- **Rate of elimination at 2 hours.**
  To find the rate of elimination (**dX/dt** = KX), you first need to determine the amount of the drug remaining at 2-hour.
  $X = Xo\ e^{-Kt}$
  $X = 500\ e^{-0.12*2}$
  X = 393.3 mg

  $\frac{dX}{dt}$ = KX
  = 0.12*393.3
  = 47.2 mg/hr

……..……..……..……..

- **Case 6**: The plasma concentration-time profile after a single IV dose of 300mg of a drug was back extrapolated and the y-intercept was 7.5mg/L

  Xo = 300 mg
  Co = 7.5 mg/L

  - **Calculate the Vd of this drug.**
    Vd = Xo/Co
    = 300/7.5
    Vd= 40 L

  - **Calculate the dose that should achieve an initial drug concentration of 12mg/L.**
    Xo = Co*Vd
    = 12*40
    Xo = 480 mg

……

- **Case 7:** After IV bolus administration of 450mg of a drug, the initial drug conc was found to be 15mg/L.

  Xo = 450 mg
  Co = 15 mg/L

  - **Calculate the Vd of this drug in this patient.**

    Vd = $\frac{Xo}{Co}$

    = $\frac{450\ mg}{15\ mg/l}$

    Vd = 30 L

- **What is the IV bolus dose required to achieve an initial drug concentration of 20mg/L?**

  Xo = Co*Vd

  = 20*30

  Xo = 600 mg

- **If the patient receives a single IV bolus dose of 2g of the drug, calculate the expected initial drug concentration after this large dose.**

  Co = $\frac{Xo}{Vd}$

  = $\frac{2000\ mg}{30\ L}$

  Co = 66.7 mg/L

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