Lecture 1
Wednesday 1 February 2023 14:12

CHAPTER 5

In this series of lectures, we look at the mathematical models used in Pharmacokinetics (PK). The fundamental aim of PK is to predict the concentration of a drug in the patient's plasma, as a function of dose and time:

$$C_p = f_{PK}(\text{Dose}, \text{time}).$$

Aim: Find f_{PK}

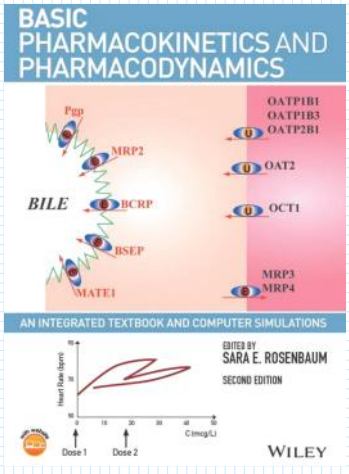
Units:

- C_p in mg/L
- Dose in mg

But this is not the whole picture. The whole picture includes pharmacodynamics, which aims to quantify the effect of a drug as a function of concentration:

$$E = f_{PD}(C_p)$$

We focus in these lectures on PK. I am not an expert on PK, interested students are referred to the recommended textbook:

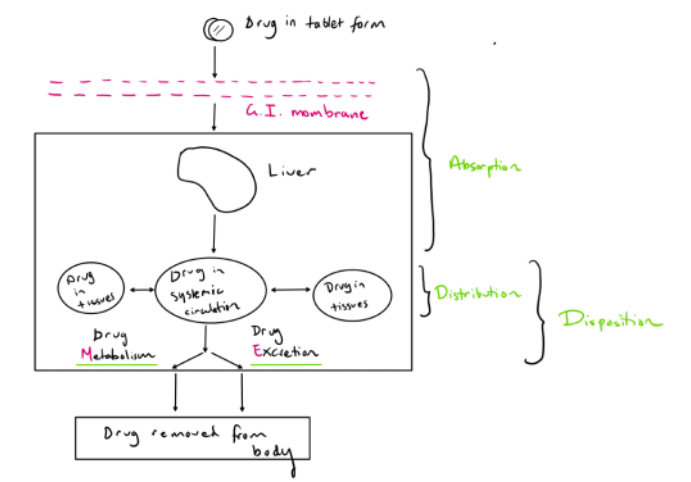


The basic processes in PK are ADME:

- Absorbed – the drug is absorbed into the bloodstream;
- Distributed – distribution to the various tissues in the body;
- Metabolized – the breakdown of a drug into other compounds (metabolites) in the liver;
- Excreted – elimination through the liver and/or kidneys.

The processes in ADME in case of oral administration

are shown in the figure below:



Plasma concentration (§5.1.1)

Plasma concentration is what gets measured in the lab. So this is what we try to quantify in our models.

Simplest Possible PK Model (§5.2)

Here we look at:

- Intravenous administration
- Drug is rapidly distributed to the tissues – one compartment.

Thus, there is only one compartment in the model. The model therefore seeks to describe A_B, the amount of drug (in mg) in the body, at a given time.
In general, this will follow first-order kinetics:

$$\frac{dA_B}{dt} = -kA_B$$

where k is the elimination constant.

Solution: $$A_B(t) = A_{B,0}e^{-kt} \qquad (1)$$

Here, A_{B0} is the initial amount present in

the bloodstream at $t = 0$. This is:

$$A_{B,0} = S \cdot D$$

- S – Salt factor: The dose is not 100% pure drug it's a mixture of pure drug + conjugate acid/base.
  Example: Quinidine Sulfate is 82% quinidine and 18% sulfate, so $S = 0.82$.
- D is the dose, in mg.

The concentration of drug in the plasma is:

$$C_p = \frac{A_B}{V}$$

where V is the volume of blood in the plasma.

Re-write Eqn (1):

$$-\frac{dA_B}{dt} = k \frac{A_B}{V} V$$

Identify:

- $Cl = kV$ CLEARANCE
- $C_p = A_B/V$.

Ao:

$$\boxed{-\frac{dA_B}{dt} = Cl \cdot C_p}$$

Furthermore,

$$C_p(t) = \frac{A_{B,0}}{V} e^{-kt}$$

$\frac{Cl}{V} = k$

$$= \frac{S.D}{V} e^{-(Cl/V)t}$$

$$\therefore \boxed{C_p(t) = \frac{S.D}{V} e^{-(Cl/V)t}} .$$

The half-life shows:

$$C_p(t_{1/2}) = \frac{1}{2} C_p(0)$$

Hence:

$$t_{1/2} = \frac{\ln 2}{k} .$$

5.2.1 Worked Example

A 20-mg dose of a drug $S = 1$ was adminstered as an intravenous bolus injection. The drug has the following PK parameters: $k = 0.1\,\mathrm{h}^{-1}$ and $V = 20\,\mathrm{L}$. Calculate C_{p_0} and hence calcualte the plsma concentration at $3\,\mathrm{h}$.

Solution:

$$C_{p_0} = \frac{S \times D}{V} = \frac{1 \times 20\,mg}{20\,L}$$

$$\Rightarrow \boxed{C_{p_0} = 1\ mg/L} .$$

After three hours,

$$C_p(t = 3h) = C_{p_0} e^{-k \times (3h)}$$

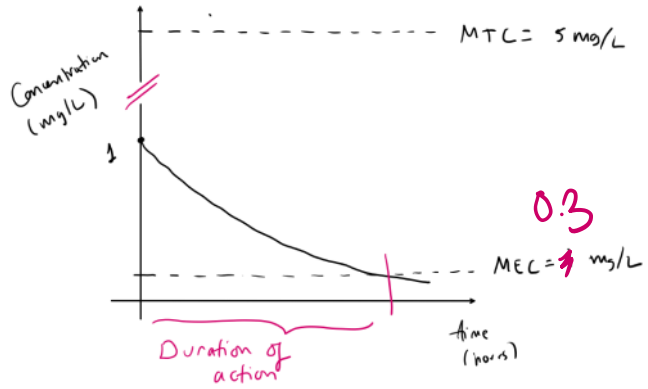
$$C_p(t=3h) = C_{p_0}\, e^{-k\times(3h)}$$

$$= \left(\frac{1\,mg}{L}\right) e^{-0.3} = 0.74\,mg/L$$

$$\Rightarrow \boxed{C_p(t=3h) = 0.74\,mg/L}$$

Carrying on with this example, if the therapeutic range is between 5 and $0.3\,\mathrm{mg}/L$, how long are the plasma concentrations in the therapeutic range?

Refer to the figure ↴



Therapeutic range superimposed over the plasma concentration-time profile

The therapeutic range refers to :

- Max therapeutic concentration (MTC) SAFETY
- Min effective concentration (MEC) EFFECTIVE

We require, at time t^* :

$$M.E.C. = C_{p_0}\, e^{-kt^*}$$

Hence,

$$0.3\,mg/L = \left(1\,mg/L\right) e^{-kt^*}$$

$\Rightarrow -\ln 0.3 = 0.1\ t_*$

Hence,

$$\boxed{t_* = 12.04\ \text{h}}$$

From this example, it can be seen that the initial Cp of $1\,\text{mg/L}$ is unsatisfactory. Therefore, calculate a dose to provide an initial plasma concentration of $5\,\text{mg/L}$.

We have:

$$C_{p_0} = \frac{S \cdot D}{V}$$

$S = 1$

$$= \frac{D}{V}$$

$$= \frac{D}{20\,\text{L}}$$

Target $= 5\ \text{mg/L}$

$\therefore\ D = (5\ \text{mg/L}) \times 20\ \text{L}$

$\Rightarrow$

$$\boxed{D = 100\ \text{mg}}$$