Lecture 3

Wednesday 1 February 2023 17:44

In this lecture, we look at other, more complicated PK models:

- Two-compartment model
- Metabolism model.

Taken from §5.4 and §5.5 of the typed notes.

We start by looking at the two-compartment model. In this model, it is assumed that the body (systemic circulation + tissues) are made up of two compartments:

- The Central Compartment, consisting of the plasma and those tissues that take up the drug rapidly;
- The Peripheral Compartment, consisting of those tissues that take up the drug more slowly.

Assumptions:

- The drug concentration measured *in vivo* is that of the central compartment.
- Elimination occurs through the well-perfused tissues, these are a part of the central compartment.

The mass balances for these processes are shown in the figure below:

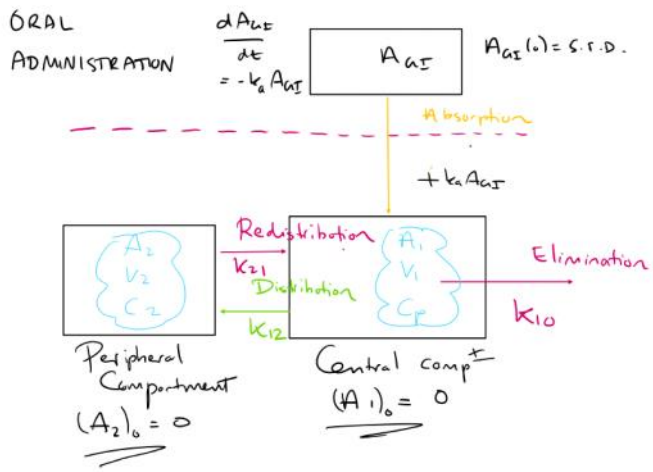
Two-compartment model:

These mass balances can be turned into a system of linear ODEs. In case of IV administration, these are:

$$\begin{aligned}\frac{dA_1}{dt} &= -k_{10}A_1 - k_{12}A_1 + k_{21}A_2,\\ \frac{dA_2}{dt} &= k_{12}A_1 - k_{21}A_2,\end{aligned}$$

ICs: $A_1(0) = S \cdot D$, $A_2(0) = 0$.

Things are more complicated in case of ORAL administration. The mass balances with the source term in the GI tract are shown in the figure below:



Mass balances for the two-compartment model (oral administration)

Again, turning these into a system of linear ODEs, we get:

$$\frac{dA_1}{dt} = \underbrace{k_a A_{GI}}_{\text{SOURCE TERM}} - k_{10}A_1 - k_{12}A_1 + k_{21}A_2,$$
$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2.$$

The ICs are:

$$A_1(0) = 0, \quad A_2(0) = 0.$$

The source term satisfies $dA_{GI}/dt = -k_a A_{GI}$, from which we get (as before):

$$A_{GI}(t) = (S.F.D)e^{-k_a t}.$$

We also look at a **Metabolism Model** (§5.5)

Here, we again use compartmental models. Metabolites of the drug are usually formed by a first-order

of the drug are usually formed by a first-order reaction in the liver. Since the liver is usually regarded as being in the central compartment, the central compartment of the metabolite is attached to the central part of the parent drug. Hence, a simple mathematical model for metabolism requires:

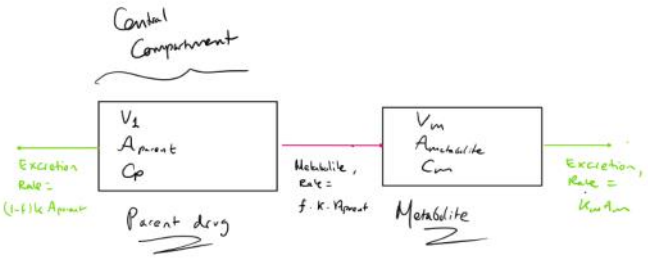
- One central compartment, volume V_1, drug amount A_{parent} and plasma concentration

$$C_p = A_{parent} / V_1$$

We look at a simple case including IV administration. Furthermore:

- The parent drug decays at rate k according to first-order kinetics, a fraction $(1 - f)$ of the drug is excreted and a fraction f is converted to metabolite;
- The metabolite is excreted at a rate k_m.

The mass balances are shown below:



Mass balances for the metabolite model (IV administration)

These are converted to equations as follows:

$$\frac{dA_{parent}}{dt} = -kA_{parent},$$
$$\frac{dA_{metabolite}}{dt} = fkA_{parent} - k_m A_{metabolite}.$$

Initial conditions:

$A_{parent}(0) = S.D$, $A_{metabolite}(0) = 0$.