Lecture 2

Wednesday 1 February 2023 14:58

In this lecture we look at Oral Administration (§5.3)

In oral administration, the drug has to pass through the gastro-intenstinal (GI) tract before making it to the circulation. The drug concentration in the GI tract is governed by first-order kinetics:

$$\frac{\mathrm{d}A_{GI}}{\mathrm{d}t} = -k_a A_{GI}, \quad (1)$$

← Not a compartment!

where $A_{GI}(t=0) = S \cdot F \cdot D$, where:

- S is the salt factor;
- F is the bioavailability – not all of the drug that passes the GI membrane
- D is the dose.

We solve (1) with the given initial conditions to get:

$$A_{GI}(t) = S \cdot F \cdot D\, e^{-k_a t} \quad (2)$$

Equation (2) then gets fed into a one-compartment model for the systemic circulations and tissue, all lumped together. This manifests itself as an extra source term in the one-compartment model:

$$\frac{dA_B}{dt} = \begin{pmatrix} \text{Drug} \\ \text{into} \\ \text{Compartment} \end{pmatrix} - \begin{pmatrix} \text{Drug out} \\ \text{of} \\ \text{compartment} \end{pmatrix}$$

$$= \text{Absorption} - \text{Elimination}$$

$$= k_a A_{GI} - k A_B$$

NEW SOURCE TERM

Hence:

$$\frac{dA_B}{dt} = k_a A_{GI} - k A_B$$

.

Or:

$$\frac{dA_B}{dt} + k A_B = k_a (S.F.D) e^{-k_a t} \quad (3)$$

Eqn (3) can be solved using the integrating-factor technique. As such, multiply Eq. (3) by e^{kt}:

$$e^{kt}\left(\frac{dA_B}{dt} + k A_B\right) = k_a (S.F.D)\, e^{(k-k_a)t}$$

L.H.S. can be re-written as:

$$\frac{d}{dt}\left(A_B e^{kt}\right).$$

So we have:

$$\frac{d}{dt}\left(A_B e^{kt}\right) = k_a (S.F.D)\, e^{(k-k_a)t}$$

Integrate:

$$A_B e^{kt}\Big|^t = k_a (S.F.D) \int^t e^{(k-k_a)t}\, dt$$

$$A_B e^{kt}\Big|_{t=0}^{t} = k_a (S.F.D) \int_0^t e^{(k-k_a)t}\, dt$$

$A_B(0) = 0$ (drug in GI tract up to $t=0$).

Hence:

$$A_B(t) e^{kt} = \frac{k_a (S.F.D)}{k-k_a} e^{(k-k_a)t}\Big|_0^t$$

$$= \frac{k_a}{k-k_a} (S.F.D) \left[e^{(k-k_a)t} - 1 \right]$$

Cancel across by e^{kt}:

$$A_B(t) = \frac{k_a}{k-k_a} (S.F.D) \left[e^{-k_a t} - e^{-kt} \right] \quad (4)$$

5.3.2 Worked Example

The plasma concentration-time data for a drug administered to a healthy volunteer are shown in Table 5.1; the dose is $D = 100\,\mathrm{mg}$. Analyze the data and determine k, k_a. Take $S = 1$.

Time (h)	Cp (mg/L)
0	0
0.6	2.74
0.8	3.13
1	3.37
1.4	3.55
1.8	3.5
2	3.43
2.6	3.12
3	2.89
4	2.33
7	1.17
12	0.37

Table 5.1: Plasma concentration of a drug at various times after the adminstration of a 100-mg oral dose

Solution: We need first of all to convert the model (for A_B) into a plasma concentration (C_p). We introduce an "effective volume" such that:

$$\frac{\text{Amount of Drug in Body}}{\text{Effective Volume of Plasma}} = \frac{\text{Amount of Drug in Plasma}}{\text{True Volume of Plasma}}$$

OR

$$\frac{A_B}{V_d} = C_p.$$

The effective volume V_d is called the volume of distribution.

Referring back to Eqn(4), we have:

$$C_p(t) = \frac{k_a}{k_a - k} \frac{D}{V_d/F} \left(e^{-kt} - e^{-k_a t} \right) \quad (5)$$

where we have taken $S = 1$.

We therefore have:

- A model, eq^{n} (5), with three parameters:

$$\underline{x} = (k_a, k, V_d/F)$$

- Data in table (Table 5.1)

We fit the model to the data using nonlinear least squares — like in the lectures on [PJ]. We use a cost function:

$\phi = V_d/F$

$$J(\underline{x}) = J(k_a, k, \phi)$$

$$= \sum_{i=0}^{N} \left\{ \begin{array}{l} \log\left[C_p^{\text{model}}(t_i) + \epsilon \right] \\ - \log\left[C_p^{\text{data}}(t_i) + \epsilon \right] \end{array} \right\}^2$$

where t_i is time in hours.

Sample Matlab code is given in the typed notes, in listings:

```
function [ka,k,Vd_F]=get_params()

[t_data,Cp_data]=get_data();
% Dose is given.
D=100;

% Create an anonymous function handle to the MATLAB file.
f = @(x)mycost(x);

% Initial guess - ka,k,Vd_F
x0 = [2,0.1,20];

lb=[0,0, 0];
ub=[10,10,200];

options = optimoptions('fmincon','Display','iter');
[x, fval] = fmincon(f,x0,[],[],[],[],lb,ub,[],options);

ka=x(1);
k=x(2);
Vd_F=x(3);
```

Results:

Parameter	Value
k_a	$1.50\,\text{hours}^{-1}$
k	$0.23\,\text{hours}^{-1}$
V_d/F	$20.0\,\text{L}$

} Fitting Parameters

Table 5.2: Estimated values of k_a, k, and V_d/F for the one-compartment model (oral administration)

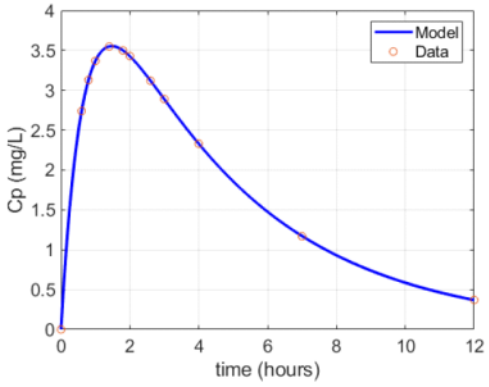

Figure 5.3: Concentration versus time curve

It is important to know what is the "area under the curve" (AUC) as it quantifies the total exposure of the patient to the drug:

$$A.U.C. = \int_0^\infty C_p(t)\,dt$$

$$\mathcal{L}\{C_p(s)\} = \frac{k_a}{k_a - k}\,\frac{D}{V_d/F}\left(\frac{1}{k} - \frac{1}{k_a}\right)$$

From the fitting parameters, we get:

From the fitting parameters, we get:

$$A.U.C. = 21.6 \text{ mg} \cdot \text{h/L}$$

The clearance is k x Volume:

$$Cl = k V_d$$

Hence,

$$\frac{Cl}{F} = k \left(\frac{V_d}{F} \right)$$

From the fitting parameters,

$$\frac{Cl}{F} = 4.62 \text{ L/h}$$