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Note

Concentration at steady-state after periodic and non-uniform administration of drug

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Abstract

A two-compartment model, with absorption from the gut and elimination from both compartments, is considered in order to express the concentration at any time and at steady-state when a drug is administered repeatedly according to a dosing schedule non-uniformly distributed over a 24-h interval. A time-delay is included to take into account the drug crossing from the gut to the central compartment.

Keywords: Periodic administration; Steady-state; Area under curve; Compartmental model; Laplace transform

1. Introduction

Several papers [1-4] have shown that it may be of interest to allow that elimination is possible from any compartment of a pharmacokinetic model, as well for a unique dose as for multiple dosing, often at regular intervals. The peripheral compartment may be used to simulate the behaviour of an active metabolite or for biliary excretion.

This paper takes into account a two-compartment model with absorption from the gut and elimination from both compartments when any amount D_i of drug are given at non-uniformly distributed times T_i over a 24-h interval, with a reproducible disposition throughout any number of days.

The model allows the determination of concentration at steady-state and it may be extended to three or more compartments [5].

2. Theoretical

2.1. The compartment model

All kinetics are order one in the compartmental model displayed in Fig. 1. The drug is administered in compartment G where absorption occurs after a time-delay τ. Each day, p various doses of an amount D_i of drug are given at various times T_i ($i = 1$ to p) with a 24-h period, during n days; F is a bioavailability factor.

Thus, the intake of the drug is described by Table 1.

2.2. The input function E(t) in compartment 1

Let us denote by $f(t-a)_+$ any function f whose value is 0 if $t < a$, for any positive number a.Then

$$E(t) = Fk_a \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} D_i e^{-k_a(t-T_i-\tau-24m)_+}$$

where k_a is the absorption coefficient from the gut to compartment 1.

2.3. The mathematical model

Let $X_i(t)$, for $i = 1$ or 2, the amount of drug at time t in compartment i. Then

$$X_1'(t) = -(k_{10} + k_{12})X_1(t) + k_{21}X_2(t) + E(t) \quad (1)$$

$$X_2'(t) = k_{12}X_1(t) - (k_{20} + k_{21})X_2(t) \quad (2)$$

with $X_1(0) = X_2(0) = 0$

If $z_i(s)$ denotes the Laplace transform of $X_i(t)$ we get

$$z_1(s) = Fk_a \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} \frac{D_i(s + k_{21})e^{-s(T_i+\tau+24m)}}{(s + k_a)(s + \lambda)(s + \mu)} \quad (3)$$

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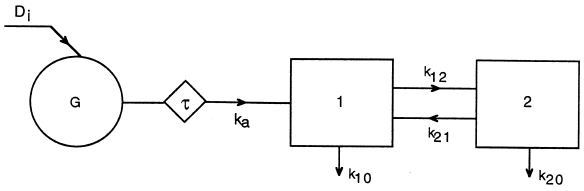

Fig. 1. A two-compartment model with administration of doses D_i in the gut G and a time-delay τ between G and the central compartment. Elimination occurs from both compartments.

where $(-\lambda)$ and $(-\mu)$ are the two roots of the following equation

$$s^2 + s(k_{10} + k_{12} + k_{20} + k_{21}) + k_{10}(k_{20} + k_{21}) + k_{12}k_{20} = 0 \tag{4}$$

Using Heaviside's theorem and putting

$$W_1 = \frac{k_{21} - k_a}{(\lambda - k_a)(\mu - k_a)}$$

$$W_2 = \frac{k_{21} - \lambda}{(k_a - \lambda)(\mu - \lambda)}$$

$$W_3 = \frac{k_{21} - \mu}{(k_a - \mu)(\lambda - \mu)}$$

we get the following expression for the concentration $C(t)$ in compartment 1 whose distribution volume is V at any time t

$$C(t) = \frac{Fk_a}{V} \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} D_i \Big[W_1 e^{-k_a(t - T_i - \tau - 24m)_+} + {}_2\, e^{-\lambda(t - T_i - \tau - 24m)_+} + W_3 e^{-\mu(t - T_i - \tau - 24m)_+} \Big] \tag{5}$$

For compartment 2

$$z_2(s) = Fk_a \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} \frac{D_i k_{12} e^{-s(T_i + \tau + 24m)}}{(s + k_a)(s + \lambda)(s + \mu)}$$

Thus, to obtain the concentration in the peripheral compartment 2, we have only to replace W_1, W_2 and W_3 in Eq. (5) by

$$W_1 = \frac{k_{12}}{(\lambda - k_a)(\mu - k_a)}$$

Table 1
Intake of the drug

Doses	FD_1	FD_2	FD_p
Times (h)			
Times in day 0	T_1	T_2	T_p
Times in day 1	$T_1 + 24$	$T_2 + 24$	$T_p + 24$
Times in day n	$T_1 + 24n$	$T_2 + 24n$	$T_p + 24n$

$$W_2 = \frac{k_{12}}{(k_a - \lambda)(\mu - \lambda)}$$

$$W_3 = \frac{k_{12}}{(k_a - \mu)(\lambda - \mu)}$$

and V by the distribution volume of compartment 2.

2.4. Concentration at steady-sate

Let $t = T + 24n$, where T stands for the time elapsed since the $(n+1)^{\text{th}}$ administration of any dose D_i during day J_n.

With $j = n - m$, we obtain for the concentration at time T in day J_n

$$C_n(T) = \frac{Fk_a}{V} \sum_{i=1}^{p} D_i \Bigg[W_1 e^{-k_a(T - T_i - \tau)} \sum_{j=0}^{n} \left(e^{-24k_a}\right)^j + W_2 e^{-\lambda(T - T_i - \tau)} \sum_{j=0}^{n} \left(e^{-24\lambda}\right)^j + W_3 e^{-\mu(T - T_i - \tau)} \sum_{j=0}^{n} \left(e^{-24\mu}\right)^j \Bigg] \tag{6}$$

The concentration at steady-state is characterised by $C_{ss}(T) = \lim_{n\to\infty} C_n(T)$. Thus

$$C_{ss}(T) = \frac{Fk_a}{V} \sum_{i=1}^{p} D_i \Bigg[\frac{W_1 e^{-k_a(T - T_i - \tau)}}{1 - e^{-24k_a}} + \frac{W_2 e^{-\lambda(T - T_i - \tau)}}{1 - e^{-24\lambda}} + \frac{W_3 e^{-\mu(T - T_i - \tau)}}{1 - e^{-24\mu}} \Bigg] \tag{7}$$

2.5. AUC calculation

If drug administration goes on to day J_n, that is during $(n+1)$ days, the area under concentration curve (AUC), from time 0 to infinity is given by

$$\text{AUC} = \frac{Fk_{21}(n+1)}{V\left[k_{10}(k_{20} + k_{21}) + k_{12}k_{20}\right]} \sum_{i=1}^{p} D_i \tag{8}$$

with $(n+1)\sum_{i=1}^{p} D_i$ standing for the total amount of administered drug. Furthermore, the AUC_{wash}, corresponding to the AUC from the time of the end of intake to the infinite, is given by

$$\text{AUC}_{\text{wash}} = \int_{24(n+1)}^{\infty} C(t)\,dt$$

Then with $u = 24(n + 1 - m) - T_i - \tau$

$$\text{AUC}_{\text{wash}} = \frac{Fk_a}{V} \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} \left[\frac{W_1}{k_a} e^{-k_a u} + \frac{W_2}{\lambda} e^{-\lambda u} + \frac{W_3}{\mu} e^{-\mu u} \right] \tag{9}$$

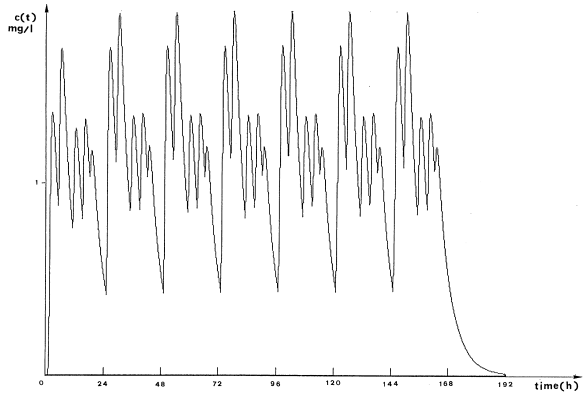

Fig. 2. An example of five administrations during 7 days of doses. $D_1 = 20$ mg; $D_2 = 15$ mg; $D_3 = 10$ mg; $D_4 = 10$ mg and $D_5 = 5$ mg at times $T_1 = 0$ h; $T_2 = 4$ h; $T_3 = 10$ h; $T_4 = 14$ h and $T_5 = 17$ h (see model parameter values in the text).

2.6. The case of intravenous administration

If we assume that the drug is directly administered in compartment 1, with the same dispositions for doses D_i, times T_i and number of days, then

Eq. (1) must be replaced by

$$E(t) = F \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} D_i \delta(t - T_i - 24m) \quad (\delta = \textit{Dirac impulse function}) \tag{10}$$

Eq. (3) must be replaced by

$$z_1(s) = F \sum_{\substack{i=1 \text{ to } p \\ m=0 \text{ to } n}} \frac{D_i(s + k_{21})e^{-s(T_i+24m)}}{(s + \lambda)(s + \mu)} \tag{11}$$

Eq. (5) must be replaced by

$$C(t) = \frac{F}{V(\mu - \lambda)} \sum_{i=1}^{p} D_i \left[(k_{21} - \lambda) \sum_{m=0}^{n} e^{-\lambda(t-T_i-24m)} - (k_{21} - \mu) \sum_{m=0}^{n} e^{-\mu(t-T_i-24m)} \right] \tag{12}$$

Eq. (7) must be replaced by

$$C_{ss}(T) = \frac{F}{V(\mu - \lambda)} \sum_{i=1}^{p} D_i \left[\frac{(k_{21} - \lambda)e^{-\lambda(T-T_i)}}{1 - e^{-24\lambda}} - \frac{(k_{21} - \mu)e^{-\mu(T-T_i)}}{1 - e^{-24\mu}} \right] \tag{13}$$

To get the same expressions for compartment 2, only $(k_{21} - \lambda)$ and $(k_{21} - \mu)$ must be replaced by k_{12} in Eqs. (12) and (13) (also V by the distribution volume of compartment 2).

3. Practical

Let us deal with the case of $p = 5$ administrations of doses D_i at times T_i during 7 days ($n = 6$) with a bioavailability factor of 70%. $D_1 = 20$ mg ; $D_2 = 15$ mg ; $D_3 = 10$ mg ; $D_4 = 10$ mg ; $D_5 = 5$ mg at times $T_1 = 0$ h; $T_2 = 4$ h; $T_3 = 10$ h; $T_4 = 14$ h; $T_5 = 17$ h.

For the following values of the model parameters: $V = 5$ l; $\tau = 1$ h; $k_a = 1.1$ h^{-1}; $k_{10} = 0.15$ h^{-1}; $k_{12} = 0.35$ h^{-1}; $k_{20} = 0.2$ h^{-1} and $k_{21} = 0.65$ h^{-1}, we get the concentration–time curve displayed in Fig. 2, by using Eq. (5).

4. Conclusion

For chronic administration of drug, with reproducible dispositions of doses and times of intake each 24 h, the proposed method enables us to get the plasma concentration at any time t, either during all days of administration or in post-intake. Furthermore, the concentration at steady-state is obtained for intravenous or oral administration.

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