European Journal of Pharmaceutics and Biopharmaceutics 45 (1998) 205–206

European Journal of Pharmaceutics and Biopharmaceutics

Letter to the Editor

Clearance and infusion

Yves Plusquellec*

UFR de Mathématiques, Université Paul Sabatier, Toulouse, France

Received 28 October 1997

Question: what must be the rate of infusion (K_o) in compartment 1 of any n-compartment pharmacokinetic model to achieve a specific steady-state concentration (C)?

Answer: $K_o = C \times Cl$ where Cl is the total clearance.

Proof: For an n-compartment pharmacokinetic model with first-order kinetics except for the input rate K_o which is constant and where elimination can take place from all compartments: let $x_i(t)$ be the amount of drug at time t in compartment i ($i = 1,\ldots,n$).

With

$$K_j = \sum_{i=0, i\neq j}^{n} k_{ji} \qquad (j = 1, \ldots, n)$$

$$\begin{cases} x'_1 = -K_1x_1 + k_{21}x_2 + \cdots + k_{n1}x_n + K_o \\ x'_2 = k_{12}x_1 - K_2x_2 + \cdots + k_{n2}x_n \\ \vdots \\ x'_n = k_{1n}x_1 + k_{2n}x_2 + \ldots - K_nx_n \end{cases} \tag{1}$$

with $x_i(o) = 0$ for all $i = 1, \ldots, n$. Coefficient k_{ij} (in time^{-1}) stands for exchange from compartment i to compartment j (k_{io} for outside).

The matrix M of this differential system is

$$M = \begin{pmatrix} -K_1 & k_{21} & & k_{n1} \\ k_{12} & -K_2 & \cdots & k_{n2} \\ \vdots & & & \\ k_{1n} & k_{2n} & \cdots & -K_n \end{pmatrix} \text{--- } \Delta$$

where Δ is the matrix obtained from M by discarding the first row and the first column of M.

* UFR de Mathématiques, Université Paul Sabatier, 118, route de Narbonne, 31062 Toulouse Cédex, France.

Let $z_i(s) = L\, x_i(t)$, the Laplace transform of $x_i(t)$. Then Eq. (1) becomes

$$\begin{cases} sz_1 = -K_1z_1 + k_{21}z_2 + \cdots + k_{n1}z_n + (K_o/s) \\ \vdots \\ sz_n = k_{1n}z_1 + \cdots - K_nz_n \end{cases} \tag{2}$$

Thus, by Cramer's method

$$z_1(s) = \frac{1}{P_M(s)} \begin{vmatrix} -K_o/s & k_{21} & \cdots & k_{n1} \\ 0 & -K_2 - s & & k_{n2} \\ \vdots & & & \\ 0 & k_{2n} & \cdots & -K_n - s \end{vmatrix}$$

where $P_M(s) = \det(M - sI_n)$ with I_n the unity matrix of order n.

Developing from the first column, we obtain

$$z_1 = -\frac{K_o}{sP_M(s)} \det(\Delta - sI_{n-1}) = \frac{P(s)}{Q(s)} \tag{3}$$

if $P(s) = -K_o \det(\Delta - sI_{n-1})$ and $Q(s) = sP_M(s)$

From Heaviside's theorem if all eigenvalues of M are distinct

$$x_1(t) = \frac{P(o)}{Q'(o)} + \sum_i \frac{P(\lambda_i)}{Q'(\lambda_i)} e^{\lambda_i t} \tag{4}$$

where λ_i are the roots of $P_M(s)$ that is the eigenvalues of M, whose real parts are always negative, such as

$$\lim_{t\to+\infty} e^{\lambda_i t} = 0$$

Thus, at steady state

$$\lim_{t\to+\infty} x_1(t) = \frac{P(o)}{Q'(o)} = \frac{-K_o \det \Delta}{P_M(o)} = \frac{-K_o \det \Delta}{\det M}$$

(Note that if the eigenvalues of M are not distinct, the result for lim $x_1(t)$ remains valid because Bromwich's theorem

0939-6411/98/$19.00
PII S0939-6411(98)00016-2

gives the same constant coefficient $P(o)/Q'(o)$, while other entries include products of t and $e^{\lambda_i t}$ whose limit when $t \to +\infty$ is 0).

If V denotes the volume of distribution of compartment 1 and $C_1(t)$ the concentration in this compartment, then

$$\lim_{t\to+\infty} C_1(t) = \frac{-K_o \det \triangle}{V \det M} \tag{5}$$

For the concentration at steady state to have a specific value C, then Eq. (5) gives the value of the necessary infusion rate K_o

$$K_o = C \times \left(\frac{-V \det M}{\det \triangle}\right) \tag{6}$$

To obtain the complete solution to the problem, it remains to show that $-V \det M/\det \Delta$ represents the total clearance.

Since clearance does not depend on the route of administration in the model, we may obtain clearance by $Cl = D/(A \cup C_1)$ where $A \cup C_1$ is the area under concentration curve in compartment 1 after a bolus of a dose D in this compartment. Furthermore, $A \cup C_1 = Z_1(o)/V$ where $Z_1(s)$ denotes the Laplace transform of the amount $x_1(t)$ in compartment 1 receiving the bolus dose D

$$Z_1(s) = \frac{1}{P_M(s)} \begin{vmatrix} -D & k_{21} & \cdots & k_{n1} \\ 0 & -K_2 - s & & k_{n2} \\ 0 & k_{n2} & & -K_n - s \end{vmatrix}$$

$$= \frac{-D \det(\triangle - sI_{n-1})}{P_M(s)}$$

Thus

$$Z_1(o) = \frac{-D \det \triangle}{P_M(o)} = \frac{-D \det \triangle}{\det M} \quad \text{and} \quad A \cup C_1 = \frac{-D \det \triangle}{V \det M}$$

so that

$$Cl = \frac{-V \det M}{\det \triangle} \quad \text{and} \quad K_o = C \times Cl$$

Note that the units are consistent on both sides of the equation (m = mass, l = liter, h = hour): K_o is in m/h; C is a concentration in m/l; a clearance Cl is in l/h thus $C \times Cl$ is in $m/l \times l/h = m/h$ as K_o.