Arch. Pharm. Res. 3(1), 13~16(1980)

Mathematical Description of Drug Distribution in the Isolated Organ

Chong-Kook Kim

College of Pharmacy, Seoul National University, Seoul 151, Korea

(Received 16 October 1979)

Abstract□The model of an isolated organ system has been constructed to simulate the behavior of drug in the circulatory system of an acting organ or site. The model is developed on the following assumptions: The drug in the microcirculatory system cannot permeate the capillary walls. The capillary bed is modeled as a simple ideal plug flow system with and without radial concentration gradient. The mathematical model is developed from basic considerations of drug distribution with hemodynamical and pharmacokinetical meanings.

It is considered that a nonmetabolic drug substance is injected into the arterial inflow site of an isolated organ at a constant rate. The concentration of the drug in the outflow site is mathematically expressed as a function of time.

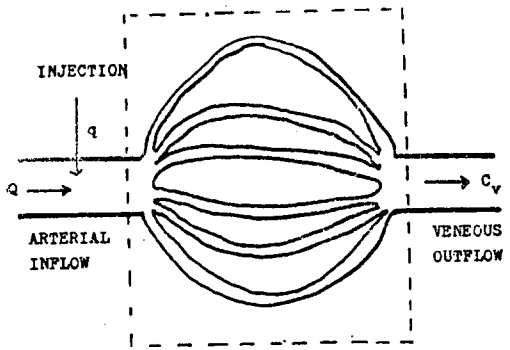
Keywords□Model—plug flow of blood; Model—radial concentration gradient; Model—drug distribution; Drug distribution—mathematical model.

Conventional pharmacokinetic models have been widely applied to simulate the kinetic behavior of drug levels in blood or plasma. However, the knowledge of drug levels in blood or plasma versus time may not provide sufficient information for adequate therapy. The kinetic information of drug levels in brain, cerebrospinal fluid, blood, organs, and tissues of pharmacological interest may be necessary for the development of more appropriate dosage regimens[1,2,3]. Drug levels in each site are influenced by the vascularity and hydrodynamic mode of blood circulation in the site[4]. Drugs are distributed in the circulatory system and are carried to the highly permeable capillaries where most of the mass transfer of drugs take place[5,6] Earlier works[7,8] concerning the hemodynamics of vascular tracers or drugs required the volume of distribution and the flow rate. The model developed and used in this study is an isolated system to simulate the behavior of drugs in the capillary of an organ or acting site. The model is developed from basic considerations of drug distribution with hemodynamical and pharmacokinetical meanings.

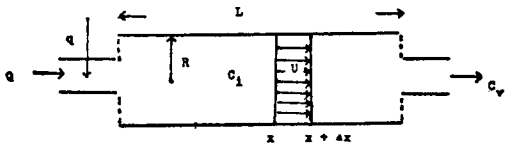
Model

The following conditions are considered: 1) Blood circulatory system is constructed with rigid capillary network which has a constant volume. 2) The drug in the microcirculatory system cannot permeate the capillary walls. 3) The capillary bed could be modeled as a simple ideal plug flow system. 4) Venous blood is not recirculated to the arterial inflow.

It is considered that, beginning at time $t = 0$, a non-metabolic drug substance is injected into the arterial inflow of an



Scheme I: Simple physical model of capillaries in the isolated organ



Scheme II: Plug flow through a capillary in the isolated organ.

isolated organ at a constant rate, q. The concentration of the drug in the venous outflow, C_v, is then measured as a function of time from t = 0 to t = ∞. The situation is simplified as described in Scheme 1.

Mathematical Description

Simple plug flow through a capillary has been modeled as shown in Scheme 2. Taking mass balance where no radial concentration gradient is assumed.

$$\frac{\partial}{\partial t}(\pi R^2 C_i \Delta X)=\pi R^2 U C_i\Big|_x-\pi R^2 U C_i\Big|_{x+\Delta x}+\left(-D\pi R^2\frac{\partial C_i}{\partial X}\right)\Big|_x-\left(-D\pi R^2\frac{\partial C_i}{\partial X}\right)\Big|_{x+\Delta x}$$

Divide by $\pi R^2 \Delta X$ and take limit,

$$\frac{\partial C_i}{\partial t}=D\frac{\partial^2 C_i}{\partial X^2}-U\frac{\partial C_i}{\partial X} \quad \cdots\cdots(1)$$

where D denotes the longitudinal diffusion coefficient of drug, U is the linear flow rate.

i) If we neglect the diffusion, then EQ(1) reduces to

$$\frac{\partial C_i}{\partial t}=-U\frac{\partial C_i}{\partial X} \quad \cdots\cdots(2)$$

which can be solved with B.C. and I.C. such that

$$\text{at } t=0,\ C_i=0,\ X\geq 0$$

$$\text{at } X=0,\ C_i=\frac{q}{Q},\ t>0$$

Taking Laplace transform, then

$$S\tilde{C}_i=-U\frac{d\tilde{C}_i}{dX} \quad \text{at } X=0,\ \tilde{C}_i=\frac{q}{QS}$$

Therefore

$$\tilde{C}_i=\frac{q}{QS}\exp\left(-\frac{S}{U}X\right)$$

Taking inverse Laplace transform,

$$C_i=\frac{q}{Q}\Upsilon\left(t-\frac{X}{U}\right) \quad \cdots\cdots(3)$$

where $\Upsilon(t)$ is an unit step function.

Therefore

$$C_v(t)=\frac{q}{Q}\Upsilon\left(t-\frac{L}{U}\right) \quad \text{where } L=\frac{V}{\pi R^2}$$

$$C_v(t)=\frac{q}{Q}\Upsilon\left(t-\frac{V}{U\pi R^2}\right) \quad \cdots\cdots(4)$$

ii) Diffusion is taken into account with I.C. and B.C. such that

$$\text{at } t=0,\ C_i=0$$

$$X=0,\ C_i=\frac{q}{Q},\ t>0$$

$$X=\infty,\ C_i \text{ is finite}$$

Taking Laplace transform of EQ(1).

$$S\tilde{C}_i=D\frac{d^2\tilde{C}_i}{dX}-U\frac{d\tilde{C}_i}{dX^2}$$

$$\text{B.C.: } X=0,\ \tilde{C}_i=\frac{q}{QS}$$

$$X=\infty,\ \tilde{C}_i=\text{finite}$$

Then

$$\tilde{C}_i(X)=A\exp\left(\frac{U+\sqrt{U^2+4DS}}{2D}X\right)+B\exp\left(\frac{U-\sqrt{U^2+4DS}}{2D}X\right)\cdots\cdots(5)$$

Substituting boundary conditions, then, $A=0$, $B=\frac{q}{QS}$, therefore,

$$\tilde{C}_i(X)=\frac{q}{QS}\exp\left(\frac{UX}{2D}\right)\exp\left(-\frac{\sqrt{U^2+4DS}}{2D}X\right)\cdots\cdots(6)$$

Let $U^2+4DS=Z$, $S=\frac{Z-U^2}{4D}$

$$\tilde{C}_i(X,Z)=\frac{4Dq}{Q(Z-U^2)}\exp\left(\frac{-\sqrt{Z}}{2D}X\right)\exp\left(\frac{UX}{2D}\right)\cdots\cdots(7)$$

Taking inverse Laplace transform of EQ(7) using convolution,

$$C_i(X,t)=\frac{4Dq}{Q}\exp\left(\frac{UX}{2D}\right)\int_0^t F(t-\tau)\mathcal{L}^{-1}\left(\exp\left(-\frac{Z}{2D}\right)\right)\cdots\cdots(8)$$

where

$$F(t)=\mathcal{L}^{-1}\left[\frac{1}{Z-U^2}\right]=\exp(U^2t)$$

$$\mathcal{L}^{-1}(\exp(-k\sqrt{Z}))=\frac{k}{2\sqrt{\pi t^2}}\exp\left(-\frac{k^2}{4t}\right)$$

Therefore

$$C_i(X,t)=\frac{4Dq}{Q}\exp\left(\frac{UX}{2D}\right)\int_0^t\exp[U^2(t-\tau)]\frac{1}{4D\sqrt{\pi\tau}}\exp\left(\frac{-X}{16D^2\tau}\right)d\tau\cdots\cdots(9)$$

If we rewrite EQ(9)

$$C_i(X,t)=\frac{q}{Q}\exp\left(\frac{UX}{2D}\right)\int_0^t\exp[U^2(t-\tau)]\frac{1}{\sqrt{\pi\tau}}\exp\left(-\frac{X}{16D^2\tau}\right)d\tau\cdots\cdots(10)$$

In a single ideal plug-flow system with the assumption of no radial concentration gradient, therefore, the concentration of the drug in the outflow site will be simplified as follows.

$$C_v(t)=\frac{q}{Q}\exp\left(\frac{UL}{2D}\right)\int_0^t\exp\left[U^2(t-\tau)-\frac{L}{16D^2\tau}\right]\frac{1}{\sqrt{\pi\tau}}d\tau\cdots\cdots(11)$$

Under this situation, the concentration of a non-metabolic drug in the outflow site has a step profile after some lag period, $t = V/Q$, based on EQ(4) and EQ(11) as shown in Figure 1.

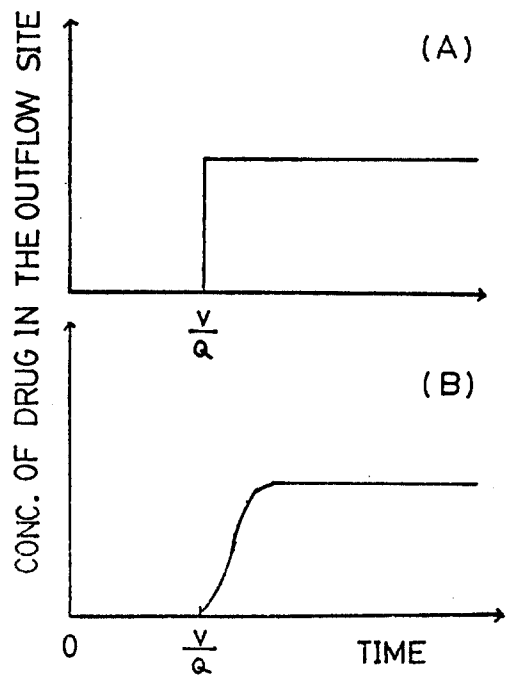


Fig. 1: The concentration of drug in the venous outflow site. Plug flow without (A) and with (B) radial concentration gradient.

LITERATURE CITED

1) Kim, C. K., and Kim, Y. B., Mathematical description of the volume of distribution in the isolated organ. *J. Korean Pharm. Sci.* **10,** 1(1980).
2) Chen, C. V., Coleman, D. L., Andrade, J. D., and Temple, A. R., Pharmacokinetic model for salicylate in cerebrospinal fluid, blood, organs and tissues. *J. Pharm. Sci.* **67,** 38(1978).
3) Bischoff, K. B., and Dedrick, R. L., Thiopental pharmacokinetics. *J. Pharm. Sci.* **57,** 1346(1968).
4) Gibaldi, M., *"Biopharmaceutics and Clinical Pharmacokinetics"*, 2nd Ed., Lea & Febiger, Philadelphia(1977).
5) Harris, E. J., *"Transport and Accumulation in Biological System"*, Butterworths, England(1960).
6) *"Active Transport and Secretion"*, Symposia of the Society for Experimental Biology, Cambridge Univ. Press, England(1954).
7) Bischoff, K. B., and Brown, R. G., Drug distribution in mammals. *Chem. Eng. Prog. Symp. Ser.* No. 66, Vol. 62, 32(1966).
8) Bischoff, K. B., in *"Chemical Engineering in Medicine and Biology"*, p. 417, Hershey, D., Ed., Plenum Press, New York(1967).