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Mathematical Description of the Volume of Distribution in the Isolated Organ

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The model of an isolated organ system has been developed to simulate the kinetic behavior of drug levels in an acting organ or site. The model is developed from basic considerations of drug distribution with hemodynamical and pharmacokinetical meanings. Model: It is considered a situation in which non-metabolic drug substance is injected into the arterial inflow of an isolated organ at constant rate. The volume of distribution and the concentration of drug in the venous outflow can be mathematically expressed as a function of time.

Blood or plasma drug levels have been used as an index of dose scheduling for therapeutics under the assumption that the drug level in blood or plasma corresponds to the pharmacological effect of the drug. 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[1-3]. 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[5-7] Earlier works[8,9] concerning the hemodynamics of vascular tracers or drugs required the volume of distribution and flow rates.

The model developed and used in this study is an isolated system to simulate the kinetic behavior of drug levels in an acting organ or site. The model is developed from basic considerations of drug distribution with hemodynamical and pharmacokinetical meaning.

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Model

It is considered a situation in which, beginning at time $t=0$, non-metabolic drug substance is injected into the arterial inflow of an isolated organ at a constant rate, q. The concentration of drug in the venous outflow is then measured as a function of time from $t=0$ to $t=\infty$. It is assumed that venous blood is not recirculated to the arterial inflow and that the drug in the organ is not uniformly distributed. The situation is simplified in Figure 1.

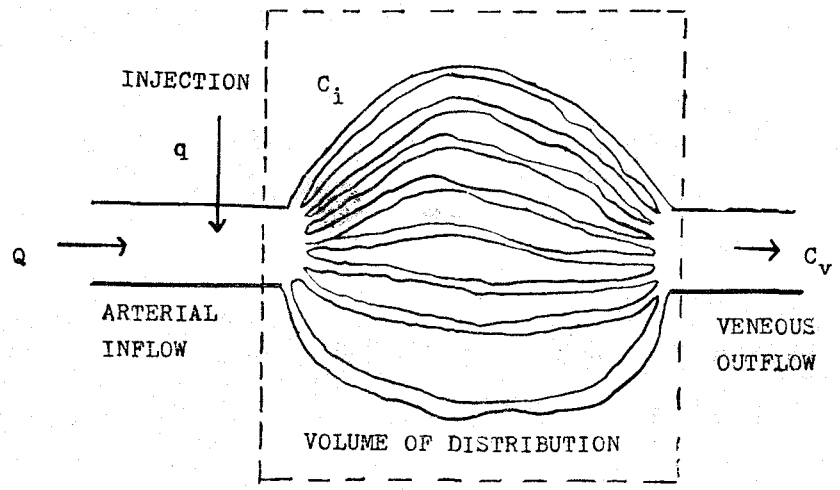

Figure 1— Simple Physical Model of Capillareis in the Isolated Organ

Mathematical Description

Taking mass balance, then

$$\frac{d}{dt}\int_v C_i dV = q - QC_v \quad \cdots\cdots(1)$$

where Q denotes the flow rate; V is the volume of distribution;
C_i is the concentration of drug in an isolated organ;
C_v is the concentration of drug in venous outflow.
Let $\overline{C_i}$ be a mean concentration of drug in the organ, then

$$\overline{C_i} = \frac{1}{V}\int_v C_i\, dV \quad \cdots\cdots(2)$$

Then, EQ(1) is reduced to

$$V\frac{d}{dt}\overline{C_i} = q - QC_v \quad \cdots\cdots(3)$$

Since we can easily guess that $\overline{C_i}$ approaches to q/Q as $t\to\infty$, C_v will also approach

to its maximum value, C_{vmax} as $t \to \infty$, unless there is specific metabolic reaction between drug and organ components. Hence for large t, we can find C_{vmax} from the plateau in the concentration-time curve and at that time, $d\overline{C}_i/dt = 0$.

Therefore.

$$Q = \frac{q}{C_{vmax}} \quad \cdots\cdots(4)$$

Using the fact, $\overline{C}_i = q/Q$ at $t = \infty$ and $\overline{C}_i = 0$ at $t = 0$,

integrate $EQ(3)$ from 0 to ∞ with respect to time.

$$V\left[\overline{C}_i(\infty) - \overline{C}_i(0)\right] = \int_0^{\infty} (q - QC_v)\, dt \quad \cdots\cdots(5)$$

Substitute $EQ(4)$ into $EQ(5)$ to eliminate Q, then, the volume of distribution in an isolated organ can be mathematically expressed as follows.

$$V = \frac{q}{C_{vmax}} \int_0^{\infty} \left(1 - \frac{C_v(t)}{C_{vmax}}\right) dt \quad \cdots\cdots(6)$$

EQ (6) is the general mathematical form of the volume of distribution as a function of infusion rate(q) and the concentration of drug in venous outflow (C_v).

If the drug in the organ is well-mixed,

$C_v = \overline{C}_i$ for all time

Then, $EQ(3)$ is reduced to

$$V\frac{dC_v}{dt} = q - QC_v \quad \cdots\cdots(7)$$

which is the same equation as that of well-mixed one compartment open model. The solution for C_v is

$$C_v = \frac{q}{Q}\left(1 - \exp\left(-\frac{Q}{V}t\right)\right) \quad \cdots\cdots(8)$$

and

$$C_v = \frac{q}{Q} \quad \text{for } t \to \infty$$

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