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Application of Mathematics to Certain Pharmacokinetic Equations

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Abstract**—***Mathematics has been given a significant place in pharmacy course to resolve a variety of equations in pharmacokinetics. Pharmacokinetic models consider drugs in the body to be in a dynamic state. Calculus is a significant mathematic tool for investigating drug movement quantitatively. Differential equations are used to relate the absorptions of drugs in various body organs over time. Integrated equations are regularly used to model the cumulative therapeutic or toxic reactions of drugs in the body. Differential calculus that involves finding the rate at which a variable measure is changing. In This paper we will discussed 2- compartmental model equation, 3- compartmental model equation , application of derivative and differential equations to certain pharmacokinetics equations.*

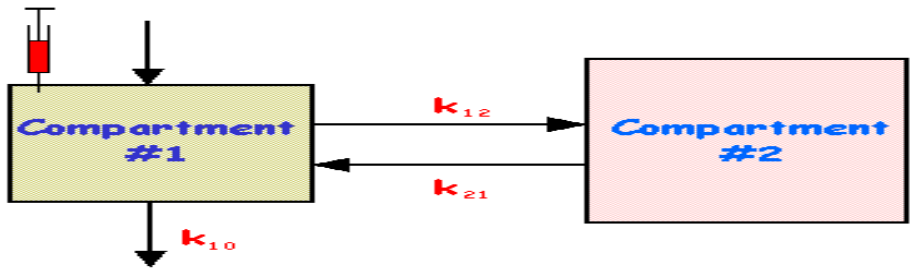
Keywords**—Ratio & Proportion, Derivative, Integration, Differential Equation, Laplace Transform, Inverse Laplace Transform, Determinant.**

I. INTRODUCTION

Pharmacokinetics refers to the rate and extent of distribution of a drug to different tissues, and the rate of elimination of the drug. Pharmacokinetics can be summarized to mathematical equations, whichever define the transfer of the drug all through the body, a net steadiness sheet from absorption and distribution to metabolism and excretion.

II. COMPARTMENTAL MODEL EQUATION

Pharmacokinetic 2-compartment model separated the body into central and peripheral compartment. The central compartment (compartment 1) consists of the plasma and tissues where the distribution of the drug is nearly instant. The peripheral compartment (compartment 2) contains a tissues wherever the supply of the drug is slower.



Figure(1)

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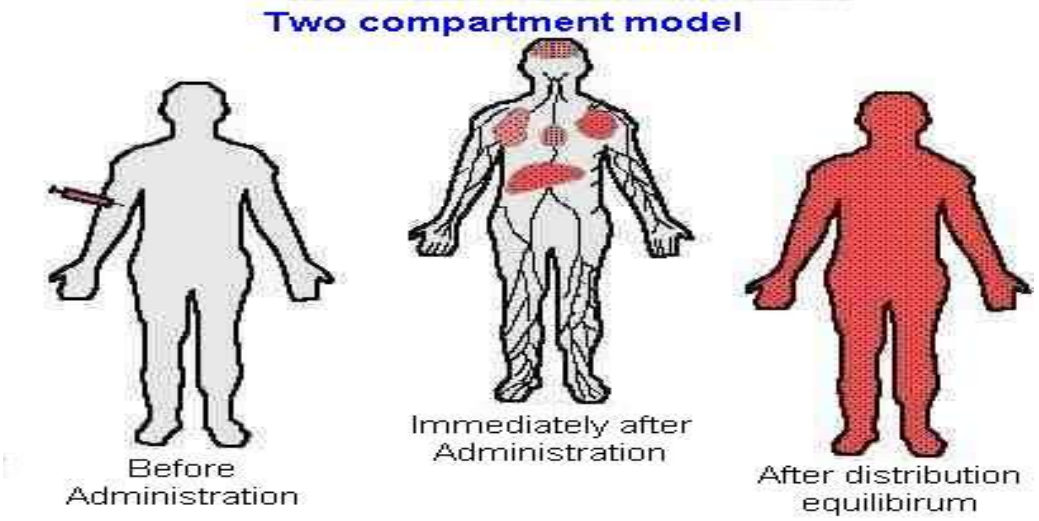

Figure(2)

In a 2- compartment model equation, distribution and elimination of a drug in a body are given by the differential equations as shown below

$$\frac{dy_1}{dt} = K_{21}y_2 - K_{12}y_1 - K_{10}y_1$$

$$\frac{dy_2}{dt} = K_{12}y_1 - K_{21}y_2$$

Applying the Laplace transform both side of the differential equation, can be transformed into Linear equations

$L\{y_1^1\} = K_{21}L\{y_2\} - K_{12}L\{y_1\} - K_{10}L\{y_1\}$

$L\{y_2^1\} = K_{12}L\{y_1\} - K_{21}L\{y_2\}$

$S\overline{y_1} - y_1(0) = K_{12}\overline{y_2} - K_{10}\overline{y_1}$

$S\overline{y_2} - y_2(0) = K_{12}\overline{y_1} - \overline{y_2}$

$(S + K_{12} + K_{10})\overline{y_1} - K_{21}\overline{y_2} = \overline{y_1}(0)$----------(1)

$-K_{12}\overline{y_1} + (S + K_{21})\overline{y_2} = 0$----------(2)

Applying Crammer's Rule to solve equation (1) and (2)

$$\Delta = \begin{vmatrix} (S + K_{12} + K_{10}) & -K_{21} \\ -K_{12} & (S + K_{21}) \end{vmatrix} = (S + K_{12} + K_{10})(S + K_{21}) - (K_{21}K_{12})$$

$$\Delta_1 = \begin{vmatrix} Dose & -K_{21} \\ 0 & (S + K_{21}) \end{vmatrix} = (Dose)(S + K_{21}) - 0$$

$$\Delta_2 = \begin{vmatrix} (S + K_{12} + K_{10}) & Dose \\ -K_{12} & 0 \end{vmatrix} = (Dose)(-K_{12})$$

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$\overline{y_1} = \frac{\Delta_1}{\Delta} = \frac{(Dose)(S+K_{21})}{(S+K_{12}+K_{01})(S+K_{21})-(K_{21}K_{12})}$

$$\overline{y_1} = \frac{(Dose)(S+K_{21})}{(S^2+S(K_{21}+K_{12}+K_{10})+K_{10}K_{21})}$$

$\overline{y_1} = \frac{\Delta_1}{\Delta} = \frac{(Dose)(S+K_{21})}{(S^2+S(a+b)+ab)}$

Put $(K_{21}+K_{12}+K_{10}) = a+b$ and $K_{10}K_{21} = ab$

$\overline{y_1} = \frac{\Delta_1}{\Delta} = \frac{(Dose)(S+K_{21})}{(S+a)(S+b)}$

III - COMPARTMENT MODEL EQUATION

Pharmacokinetic 3-compartment model separated the body into central compartment and two peripheral compartments. The central compartment (compartment 1) consists of the plasma and tissues where the distribution of the drug is essentially instant. The peripheral compartments (no. 2 and 3) contain a tissues wherever the supply of the drug is slower compared to compartment 1.

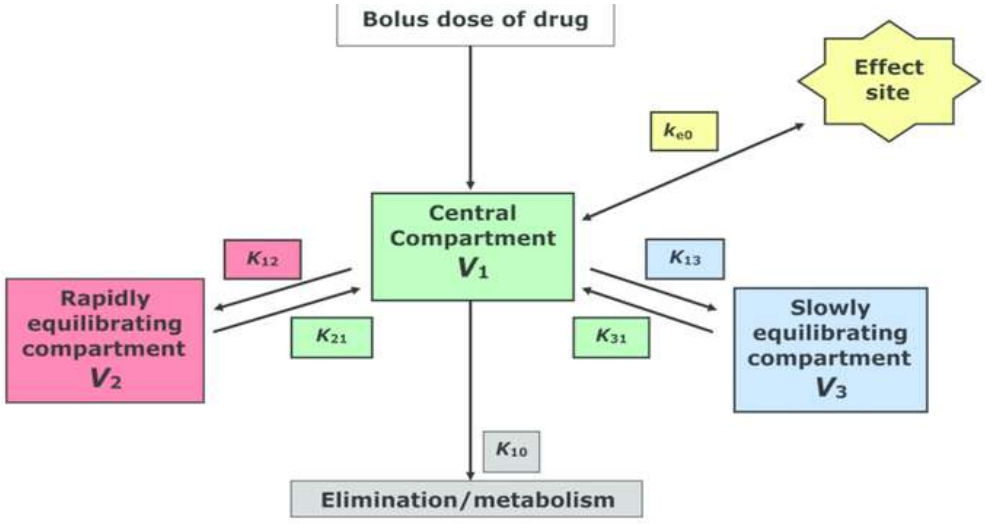

Figure (3)

In a 3- compartment model equations distribution and elimination of drug in the body is given by the differential equations as shown below

$$\frac{dy_1}{dt} = K_{21}y_2 + K_{31}y_3 - K_{12}y_1 - K_{13}y_1 - K_{10}y_1$$

$$\frac{dy_2}{dt} = K_{12}y_1 - K_{21}y_2$$

$$\frac{dy_3}{dt} = K_{13}y_1 - K_{31}y_3$$

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Applying the Laplace transform both side of the differential equation, can be transformed into Linear equations

$L\{y_1^1\} = K_{21}L\{y_2\} + K_{31}L\{y_3\} - K_{12}L\{y_1\} - K_{13}L\{y_3\} - K_{10}L\{y_1\}$

$L\{y_2^1\} = K_{12}L\{y_1\} - K_{21}L\{y_2\}$

$L\{y_3^1\} = K_{13}L\{y_1\} - K_{31}L\{y_3\}$

$Sy_1 - y_1(0) = K_{21}y_2 + K_{31}y_3 - K_{12}y_1 - K_{13}y_1 - K_{10}y_1$

$Sy_2 - y_2(0) = K_{12}y_1 - K_{21}y_2$

$Sy_3 - y_3(0) = K_{13}y_1 - K_{31}y_3$

$Sy_1 - y_1(0) = K_{21}y_2 + K_{31}y_3 - (K_{12} + K_{13} + K_{10})y_1$----------(3)

$Sy_2 - y_2(0) = K_{12}y_1 - K_{21}y_2$----------(4)

$Sy_3 - y_3(0) = K_{13}y_1 - K_{31}y_3$----------(5)

Apply Crammer's rule to solvesystems of linear equations (3),(4) and (5) to find the value of y_1

$$\Delta = \begin{vmatrix} (S + K_{12} + K_{13} + K_{10}) & -K_{21} & -K_{31} \\ -K_{12} & s + K_{21} & 0 \\ -K_{13} & 0 & s + K_{31} \end{vmatrix}$$

$=S^3 + S^2(K_{10} + K_{12} + K_{13} + K_{21} + K_{31}) + S(K_{10}K_{21} + K_{13}K_{21} + K_{10}K_{31} + K_{21}K_{31} + K_{31}K_{12}) + K_{21}K_{31}K_{10}$

$=S^3 + S^2(a + b + c) + S(ab + bc + ca) + abc$

$$\Delta_1 = \begin{vmatrix} 1 & -K_{12} & -K_{13} \\ 0 & s + K_{21} & 0 \\ 0 & 0 & s + K_{31} \end{vmatrix} = (s + K_{21})(s + K_{31})$$

$y_1 = \frac{\Delta_1}{\Delta} = \frac{(s+K_{21})(s+K_{31})}{S^3+S^2(a+b+c)+S(ab+bc+ca)+abc}$

$y_1 = \frac{\Delta_1}{\Delta} = \frac{(s+K_{21})(s+K_{31})}{(S+a)(S+b)(S+c)}$

IV. APPLICATION TO DERIVE PHARMACOKINETICS EQUATIONS

(i) After the intravenous injection of a drug to a patient, it distributing in the body and also eliminates in the body as first order kinetics is set into the differential

$\frac{dY}{dt}$=-KY, where Y is the total amount of drug in the body of a patient in time t.

Let $\frac{dY}{dt} = Y'$

Then $Y' = -KY$

Appling Laplace transform on both side

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L{Y'}=-L{$-$KY}

$\bar{Y} - Y_0 = -K\bar{Y}$

$(S\bar{Y} + K\bar{Y})$=Y

$\bar{Y} = \frac{Y_0}{S+K}$ S-Laplace operator

Then take inverse Laplace transform both side

$L^{-1}\{\bar{Y}\}=Y_0 e^{-Kt}$

Y=$Y_0 e^{-Kt}$

Thus $Y_0 -$ amount of drug given to the patient when time is zero.

V. APPLICATION OF DIFFERENTIAL EQUATION

(I) In a certain culture of bacteria, the rate at which bacteria increase is proportional to the instaneous number present. If the original number doubles in one hour, in how many hour will it triple?

N represent the number at time t

$$\frac{dN}{dt} \propto N$$

$\frac{dN}{dt} = KN$where K is positive constant

By method of one variable

$$\frac{dN}{N} = Kdt$$

$$\therefore \int_0^N \frac{dN}{N} = \int_0^N Kdt$$

logN=kt+logC

logN-logC=Kt

$\therefore \frac{N}{C}=e^{Kt}$

N=Ce^{Kt}

For t=0 then N = N_0

Put C= N_0

N=$N_0 e^{Kt}$

This gives the number of bacteria at time t$\geq 0, if\ K\ is\ known$

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It is given that N=2N_0 WHEN t=1

Then 2N_0=$N_0 e^K$

$$e^K = 2$$

Then N=$N_0 e^{Kt}$ can be written as N=$N_0 2^t$

Suppose the original triple in T (hr.).Then N = 3N_0 when t=T

Then $3N_0 = N_0 2^T$

3=2^T

log (3) = Tlog(2)

T=$\frac{\log(3)}{\log(2)} = \frac{0.4771}{0.3010}$ = 1.6 hrs.

The time of course for which the drug is administered intravenously (Infusion at a constant rate is set into the system of linear differential equation

$\frac{dP(t)}{dt}$= -k P(t) +Q_0 where P(t) – Amount of drug present at time t and Q_0 - is a drug flow rate into the compartment in units of amount/time.

By linear differential equation

The above equation should be used for solving

$\frac{dP(t)}{dt}$ + k P(t) =Q_0 (K and Q_0 are functions of t)

P(t)$e^{\int K dt} = \int Q_0 \, e^{\int K dt} dt + c$

P(t)$e^{Kt} = \int Q_0 \, e^{Kt} dt + c$

P(t)$e^{Kt} = Q_0 \left[\frac{e^{Kt}}{K}\right]_0^t$

P(t)$e^{Kt} = Q_0 \left[\frac{e^{Kt}}{K} - \frac{e^0}{K}\right]$

P(t)$e^{Kt} = \frac{Q_0}{K}\left[\frac{e^{Kt}}{K} - 1\right]$

Then P(t) = = $\frac{Q_0}{K}(1 - e^{-Kt})$

(II) **Diffusion Problem:**

Let the Cell contains constant volume of solute of concentration C_0

Let C = c(t0 be the concentration when time is t)

By diffusion the molecules of the solute will wnter the cell from the surrounding liquid

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Let m=m(t) be the mass of solute in the cell

A- Artea of the cell Menbrane

V- Volume of the cell

But m(t) = V.C(t)

According to the Fick's Law

$$\frac{dm}{dt} = KA(C_0 - c)$$

If C< C_0 then $\frac{dm}{dt}$ is directly proportional to the area of the membrane and to the difference in concentration on both side of the membrane

But $\frac{dm}{dt} = V\frac{dc}{dt}$

$\frac{dc}{dt} = \frac{1}{V}\frac{dm}{dt}$

$$\frac{dc}{dt} = \frac{KA(C_0 - c)}{V}$$

$$\frac{dc}{(C_0 - c)} = \frac{KA}{V}dt$$

$$\int \frac{dc}{(C_0 - c)} = \int \frac{KA}{V}dt$$

$\text{Log}(C - C_0) = \frac{KA}{V}t$

Apply if t =0 and t=t

$\text{Log}(C - C_0) = \frac{KA}{V}t$+K

Take exp both side

$C - C_0 = e^{\frac{KA}{V}t+\text{K}}$

$C - C_0 = e^{\frac{KA}{V}t} + e^{K}$

$C - C_0 = Ke^{\frac{KA}{V}t}$

$C = Ke^{\frac{KA}{V}t} + C_0$

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VI.CONCLUSION

Using operators like derivative, differentialequation, integration, Laplace transform, Determinants, Ratio & Proportion we can find Pharmacokinetic equations.In this paper we have proved 2-compartment model equation,3-compartment model equation, diffusion problem by application of above mentioned mathematical operators.

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