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A Mathematical Review on Open Two Compartment Pharmacokinetic Models

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ABSTRACT

This paper deals with the application of Laplace Transform to estimate the fate of a drug in the mammillary body with the prediction of various biological parameters (k, k_{12}, and k_{21}) through the method of residuals. The essential numerical values of k, k_{12}, and k_{21} are estimated through the determination of the mathematical hybrid constants (A, B, a, b, and T). Besides, these values can predict the tissue concentration (c_t) of the drug, and biological half-life ($t_{1/2}$) as well. Thus, this study provides intuitive information on the fate of the administered drug in a mammillary body, successfully.

Key words: Compartment model, Inverse transform, Laplace transform, Method of residuals, Pharmacokinetics

INTRODUCTION

The pharmacokinetic models[1-3] are used in drug concentration analysis in various biological compartments (plasma compartment, tissue compartment, deep-tissue compartment, and mammillary compartment). Among them, the mammillary compartment model is usually used for the drug distribution analysis in the biological body.[4-6] This compartment model can be divided into one, two, three, four, etc., compartment models[7] according to the drug distribution in the body. To study and understand various compartment models, the pharmacokinetic parameters are needed in the compartment model to predict the drug disposition and biological half-life of the drug. The pharmacokinetic parameters as well as biological half-life predict the distribution process and elimination process. The effective concentration of drug in the body is a must to produce a pharmacological response. If the plasma concentration of the drug declines below the effective concentration, there is no pharmacological response to treat the disease.[8] Furthermore, a higher concentration of plasma drugs produces toxic effects. Hence, the dose and dose interval are imperative fact in the administration of a drug to patients. The dosage regimen (dose and dose interval) is related to pharmacokinetic factors (absorption rate constant, elimination rate constant, and biological half-life). According to the mammillary compartment model,[9-11] when a drug is injected through the intravenous route as a bolus dose, initially all the drugs present in the plasma compartment (central compartment). However, gradually, as time increases the concentration of drugs in the central compartment declines due to the transport of the drug to the peripheral compartment. Therefore, in the central compartment, there are two phases' are present; one of them is the drug distribution phase and another one drug decline phase.[12,13] Besides, in the peripheral compartment, the drug concentration increases and finally forms an equilibrium condition with the central compartment.[14,15]

On the other hand, according to the compartment model,[16,17] at any time some fraction of drug remains in the central compartment, in the tissue compartment as well. Drug elimination occurs from the central compartment and from the peripheral compartment also.[18] Some fraction of the plasma drug is excreted from the central compartment; some fraction of the drug is metabolized in the central compartment as well. For a two compartment open models [Figure 1], the drug is distributed from the central compartment

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(plasma compartment) to peripheral compartment (tissue compartment).[19-21] The previous study on two open compartment body models did not focus on the relationship of the multiple-dosage regimens clearly.[20] Furthermore, those studies did not evaluate tissue hybrid constant (T), which is very important for drug distribution in the tissue compartment. In this study, we have focused on both the two open compartment models and method of residuals precisely through mathematical analysis. Therefore, this study gives intuitive information on dose regimen (dose and dosing intervals), which is the prerequisite for the multiple-dosage regimens drug delivery system as well as drug accumulation in the peripheral compartment (e.g., adipose tissue) of the body.

THEORY AND DISCUSSION

When a drug is administered by intravenous route as a bolus dose, the injected drug, that is, that satisfy open two compartment body models, distributes through the central compartment as well as peripheral compartment. It is assumed that the drug elimination occurs from the central compartment.[22,23]

METHODOLOGY

The mathematical formula is derived through Laplace transform.[24] The Laplace transform F = F(s) of a function f = f(t) is defined by, L(f)(s) = F(s) = $\int_0^\infty e^{-ts} f(t)dt$. The integral is evaluated with respect to t; hence, once the limits are substituted, what is left are in terms of s. Let f be a function and L(f) = F be its Laplace transform. Then, by definition, f is the inverse transform of F. This is denoted by $L^{-1}(F) = f$. As for example, from inverse Laplace transform, $L(e^{-kt}) = 1/(s+k)$; $L(1) = 1/s$ can be written in the inverse transform notation as $L^{-1}(1/(s+k)) = e^{-kt}$; $L(1/s) = 1$. On the other hand, if a function y = y(t), then the transform of its derivative dy/dt can be expressed in terms of the Laplace transform of y: L(dy/dt) = sL(y)–y(0).

Proof:

Let a drug following two-compartment model be administered to a subject. The drug elimination is occurred from the central compartment [Figure 2]. If the drug is administered as intravenous bolus dose (D_0), the drug concentration in plasma compartment and tissue compartment is c_p and c_t, respectively, at time t. The initial (t = 0) plasma concentration of the drug is C_0^p.

The change in drug concentration in plasma compartment and tissue compartment is dc_p and dc_t, respectively, with respect to time dt. Here, the elimination rate constant from the central compartment is k.

According to the chemical kinetics [Figure 2] (the drug satisfies first order kinetics),

$dc_p/dt = k_{21}c_t – c_pk_{12} – kc_p$ (1)

$dc_t/dt = k_{12}c_p – k_{21}c_t$ (2)

By adding the equation (1) and (2),

$dc_p/dt + dc_t/dt = –kc_p$ (3)

Transforming the derivatives by Laplace transform, equation (2) gives,

$sC_t(s)(t) – C_t(0) = k_{12}C_p(s)(t) – k_{21}C_t(s)(t)$

Or,

$(s+k_{21})C_t(s)(t) = k_{12}C_p(s)(t)$ (4)

$C_t(0) = 0$ (initial tissue drug concentration)

Similarly from equation (3),

$sC_p(s)(t) – C_p(0) + sC_t(s)(t) – C_t(0) = kC_p(s)(t)$

Or,

$(s+k)C_p(s)(t) + sC_t(s)(t) = C_0^p$; [Initially $C_p(0) = C_0^p$,

$C_t(0) = 0$] (5)

By solving the equation (4) and (5),

$(s+k)C_p(s)(t) + sk_{12}C_p(s)(t)/(s+k_{21}) = C_0^p$

Or, $C_p(s)(t) = C_0^p(s+k_{21})/\{(s+k)(s+k_{21})+sk_{12}\} =$

$C_0^p (s+k_{21})/\{s^2+(k_{12}+k_{21}+k)s+kk_{21}\} = C_0^p(s+k_{21})/$

$\{s^2+(a+b)s+ab\} = C_0^p (s+k_{21})/\{(s+a)(s+b)\}$

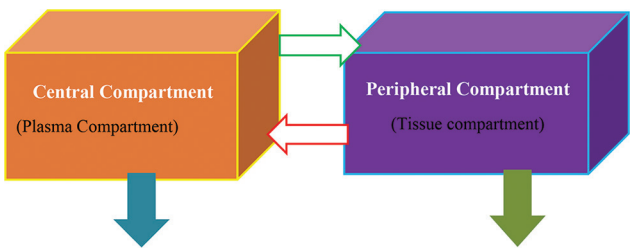

Figure 1: Open two compartment models

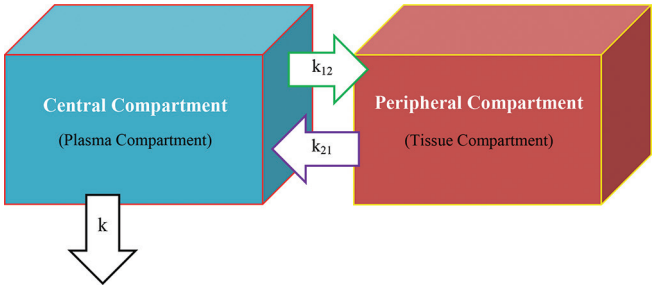

Figure 2: Open two compartment models

Here, $a+b = k_{12}+k_{21}+k$, and $ab = kk_{21}$
By performing partial fraction, we can write,
$C_p(s)(t) = C_0^p [(a–k_{21})/\{(a–b)(s+a)\}]+C_0^p [(k_{21}–b)/\{(a–b)(s+b)\}]$ (6)
Now, by applying inverse Laplace transform, we get from equation (6)
$C_p(t) = Ae^{-at}+Be^{-bt}$ (7)
where, $A = C_0^p (a–k_{21})/(a–b)$, and $B = C_0^p (k_{21}–b)/(a–b)$
Again, we get from the equations (4) and (5),
$C_t(s)(t) = k_{12} C_0^p /\{(s+k)(s+k_{21})+sk_{12}\} = k_{12} C_0^p /\{s^2+(k_{12}+k_{21}+k)s+kk_{21}\}$
So, $C_t(s)(t) = k_{12} C_0^p /(s+a)(s+b)$

By performing partial fraction the equation number,
$C_t(s)(t) = k_{12} C_0^p /\{(b−a)(s+a)\}+k_{12} C_0^p /\{(s+b)(a−b)\}$
Again, by applying the Inverse Laplace Transform,
$C_t(t) = Te^{-bt}–Te^{-at}$ (8)
where, $a+b = k+k_{12}+k_{21}$; $ab = kk_{21}$
$T = k_{12} C_0^p /(a−b)$.

Mathematical Analysis

The initial (time t = 0) plasma concentration of the drug, C_0^p tissue concentration C_t^0. We get from the equation number (7) and (9) and their hybrid constant (A, B, a, b),

$$C_p^0 = A+B \quad (9)$$

$$C_t^0 = 0 \quad (10)$$

$$k_{21} = (Ab+Ba)/(A+B) \quad (11)$$
$$k_{12} = AB(a–b)^2/\{(A+B)(Ab+Ba)\} \quad (12)$$
$$k = ab(A+B)/(Ab+Ba) \quad (13)$$
$$T = AB(a–b)/(Ab+Ba) \quad (14)$$

By putting the numerical values of hybrid constants (A, B, a, and b) in the equation number (11), (12), and (13); we can get the value of the pharmacokinetic rate constants k_{12}, k_{21}, and k. The plasma concentration and tissue concentration of the drug at any time can be determined from the equation number (6) and (7) as well.

Calculation

The numerical values of the constants (k, k_{12}, k_{21}, and $t_{1/2}$) are determined through the method of residual.[25] Now, let the data obtained by the blood sample at different intervals t_1, t_2, t_3, t_4, t_5, t_6, t_7, t_8, t_9, and t_{10}; the observed plasma concentration quantities are c_1, c_2, c_3, c_4, c_5, c_6, c_7, c_8, c_9, and c_{10}, respectively. According to the equation (7), it is obtained a non-linear curve rather than a straight line. Hence, the biexponential curve represents the distribution phase as well as the elimination phase.
Let, the interpolated data c_1, c_2, c_3 and c_8, c_9, c_{10} lies in the distribution phase curve and elimination phase curve, respectively, of the biexponential curve. According to the biexponential distribution in the plasma compartment, the initial distribution phase (Ae^{-at}) is more rapid than the elimination phase (Be^{-bt}). Hence, it is considered with the increasing time distribution phase slows down and the elimination phase proceeds rapidly and Ae^{-at} approaches to zero, and Be^{-bt} has a finite value.
Hence, it is obtained from the equation (10),
$C_p(t) = Be^{-bt}$
By taking natural logarithm in both sides,
$\ln(C_p)(t) = −bt+\ln(B)$ (i)
This equation follows the formula y = mx+c; m and c are slope and intercept (y axis), respectively, of the straight line. The numerical values of the b, B can be easily determined from elimination phase data, (c_8, c_9, and c_{10}) and (t_8, t_9, and t_9).
According to the equation (i),
$b = \{\ln(c_8)–\ln(c_9)\}/(t_9–t_8)$, and $B = c_8/e^{-bt}{}_8$,
Moreover, the elimination half-life of the drug,
$t_{1/2} = 0.693/b$ (ii)
In the distribution phase, the drug is also eliminated concurrently. Therefore, we must take into consideration the eliminated fraction of the plasma drug concentration to determine the distribution phase hybrid constants a, A. Hence, the eliminated fraction can be determined by, $C_p^{'}(t) = Be^{-bt}$,

Where, $C_p^{'}$ is obtained from the distribution phase data (c_1, c_2, and c_3). Hence, the residual plasma drug concentration is $C_p - C_p^{'}(let, C_p - C_p^{'} = C_p^{''})$ during distribution phase and the eliminated fraction drug concentration are $C_1^{'}, C_2^{'}, C_3^{'}$.

Now, it is obvious that, $C_p(t) = Ae^{-at}+Be^{-bt}$
Or, $C_p(t) = Ae^{-at}+C_p^{'}(t)$

Or, $C_p(t)−C_p^{'}(t) = Ae^{-at}$

Or, $C_p^{''}(t) = Ae^{-at}$;

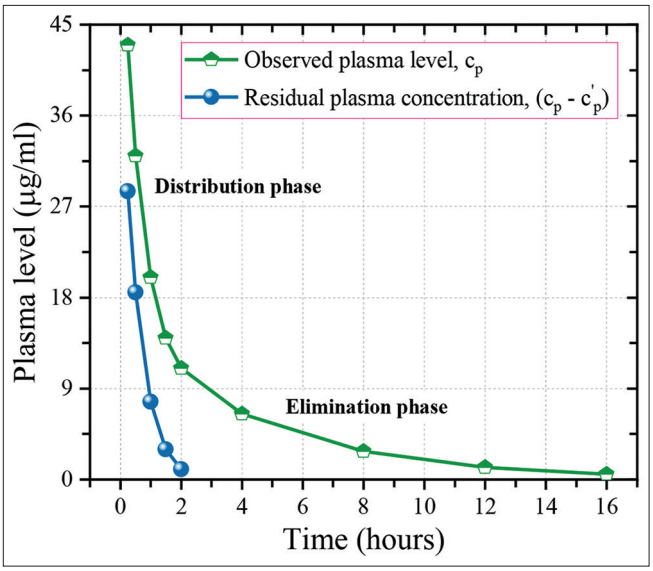

Figure 3: Plasma level-time curve for a two open compartment models

where, $C''_p(t) = C_p(t) - C'_p(t)$ is the residual plasma drug concentration

Let, the residual plasma drug concentration be C''_1, C''_2, C''_3 with respect to eliminated fraction of drug from plasma data C'_1, C'_2, C'_3 respectively. By taking the natural logarithm, it is obtained,

$$\ln(C''_p) = \ln(A) - at \qquad \text{(iii)}$$

According to the equation, $a = \{\ln(C''_1) - \ln(C''_2)\}/(t_2 - t_1)$, and $A = C''_2/e^{-at}{}_2$

The elimination half-life of the drug is calculated from the elimination phase; the hybrid constants (a, A) are determined from the distribution phase.

RESULTS

The numerical value of all the mathematical hybrid constants A, B, a, b, and T are 45, 15, 1.8, 0.21, and 29.4, respectively [Figure 3]. Therefore, the calculated value of pharmacokinetics factors k, k_{12}, and k_{21}, and the elimination half-life ($t_{1/2}$) are 0.62 h^{-1}, 0.78 h^{-1}, 0.61 h^{-1}, and 3.3 h as well. These calculated values of all parameters (k_{12}, k_{21}, k, and $t_{1/2}$) predict the fate of the administered drug.

CONCLUSION

In summary, the Laplace transform has been used to derive the formulas [$C_p(t) = Ae^{-at} + Be^{-bt}$] and [$C_t(t) = Te^{-bt} - Te^{-at}$]. Using these two formulas, we have observed that the fate of a drug is given intravenously as a bolus dose that follows open two compartment body models. We also estimated numerical values of tissue concentration, that is, deposited drug concentration in the peripheral compartment. Therefore, this present research may give effective guidance to the research community to determine the biological half-life ($t_{1/2}$) and pharmacokinetic parameters (k, k_{12}, and k_{21}) that can assist to predict the drug elimination process, drug effectiveness, and dosing intervals determination of the drug.

DECLARATION OF INTERESTS

The author declares no competing financial and non-financial interests.

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