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# A Mathematical Review to Estimate the Fate of a Drug Following Open Two Compartment Model, When it is Administered by Intravenous Route

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## ABSTRACT

This paper deals with the application of Laplace Transform [$L(f)(s) = F(s) = e^{-ts}\ f(t)dt$] to derive the formula [$(C_p(t) = Ae^{-at} + Be^{-bt}$] and [$C_t(t) = Te^{-bt} - Te^{-at}$] to estimate the fate of a drug in the mammillary body with the prediction of the biological parameters [k, $k_{12}$, and $k_{21}$]. The numerical values of [k, $k_{12}$, and $k_{21}$] which is estimated through the determination of the mathematical hybrid constants (A, B, a, b, T) also predict the tissue concentration of the drug, biological half-life as well.

**Key words:** Compartment model, Laplace transform and inverse transform, pharmacokinetics, rate constant

## INTRODUCTION

When a drug is injected through intravenous route, initially, all the drugs present in the plasma compartment (central compartment). As time increases, the concentration of drug in central compartment declines due to the transport of the drug to peripheral compartment (tissue compartment), elimination of the drug from central compartment as well. Hence, in the central compartment, there are two phases, drug distribution phase as well as drug decline phase.
In tissue compartment (peripheral compartment), the drug concentration increases and finally forms an equilibrium condition with central compartment. Hence, at any time, some fraction of drug remains in the central compartment, in tissue compartment as well. The drug elimination occurs from the central compartment, that is, some fraction of plasma drug is excreted. Moreover, some fraction of drug is metabolized in the central compartment.

## THEORY AND DISCUSSION

Methodology, when a drug is administered by intravenous route as a bolus dose, the injected drug distributes through central compartment as well as peripheral compartment. The drug elimination occurs from the central compartment.

### Laplace transform

The Laplace transform F=F(s) of a function f=f(t) is defined by , $L(f)(s) = F(s) = e^{-ts}\ f(t)\ dt$. The integral is evaluated with respect to t, hence, once the limits are substituted, what is left are in terms of s.

### Inverse Transform

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. We get that $L(e^{-kt}) = 1/(s+k)$, $L(1) = 1/s$ written in the inverse transform notation $L^{-1}(1/(s+k)) = e^{-kt}$; $L(1/s) = 1$.

### Transform of derivatives

If a function y=y(t). The transform of its derivative y' can be expressed in terms of the Laplace transform of y: $L(y') = sL(y) - y(0)$

### Proof

In my proposed mathematical analysis, I considered both the plasma and tissue compartment elimination rate constant,

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Let a drug be administered as intravenous bolus dose ($C_0^p$), the drug concentration in plasma compartment and tissue compartment is $c_p$ and $c_t$, respectively, at time t. The change in drug concentration in plasma compartment and tissue compartment is $dc_p$ and $dc_t$, respectively, with respect to time dt. The elimination rate constant from central compartment is k.

According to chemical kinetics (the drug satisfies first order kinetics),

$dc_p/dt = k_{21}c_t - c_p k_{12} - kc_p$ (1)

$dc_t/dt = k_{12}c_p - k_{21}c_t$ (2)

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

We get, $dc_p/dt + dc_t/dt = -k_p c_p$ (3)

Transforming the derivatives by Laplace transform

From Equation (2), $sC_t(s)(t) - C_t(0) = k_{12}C_p(s)(t) - k_{21}C_t(s)(t)$

Or, $(s+k_{21})C_t(s)(t) = k_{12}C_p(s)(t)$ (4); $C_t(0) = 0$ (initial tissue drug concentration)

From Equation (3),

$sC_p(s)(t) - C_p(0) + sC_t(s)(t) - C_t(0) = K_p C_p(s)(t)$

Or, $(s+k)C_p(s)(t) + sC_t(s)(t) = C_p^0$; [Initially $C_p(0) = C^0{}_p$, $C_t(0) = 0$] (5)

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

$(s+k)C_p(s)(t) + sk_{12}C_p(s)(t)/(s+k_{21}) = C_p^0$.

Or, $C_p(s)(t) = C_p^0(s+k_{21})/\{(s+k)(s+k_{21})+sk_{12}\}$

$= C_p^0(s+k_{21})/\{s^2+(k_{12}+k_{21}+k)s+kk_{21}\}$

$= C_p^0(s+k_{21})/\{s^2+(a+b)s+ab\}$

Here, $a+b = k_{12}+k_{21}+k$

$ab = kk_{21}$

By performing partial fraction,

We get, $C_p(s)(t) = C_p^0[(a-k_{21})/\{(a-b)(s+a)\}] + C_0^p[(k_{21}-b)/\{(a-b)(s+b)\}]$

By applying inverse Laplace transform,

We get from Equation (6)

$C_p(t) = Ae^{-at} + Be^{-bt}$ (6)

Where, $A = (a-k_{21})/(b-a)$

$B = (k_{21}-b)/(a-b)$

Again we get from the Equations (4) and (5)

$C_t(s)(t) = k_{12}C_p^0/\{(s+k)(s+k_{21})+sk_{12}\}$

$= K_{12}C_p^0/\{s^2+(k_{12}+k_{21}+k)s+kk_{21}\}$

So, $C_t(s)(t) = k_{12}C_p^0/(s+a)(s+b)$

By performing partial fraction, the equation number,

We get, $C_t(s)(t) = k_{12}C_p^0/(b-a)(s+a) + k_{12}C_p^0/(s+b)(a-b)$

By applying the inverse Laplace transform,

We get, $C_t(t) = Te^{-bt} - Te^{-at}$ (7)

Where, $a+b = k+k_{12}+k_{21}$; $ab = kk_{21}$

$T = k_{12}C_p^0/(a-b)$.

## MATHEMATICAL ANALYSIS

The initial (time t = 0) plasma concentration of the drug, $C_p^0$ tissue concentration $C_t^0$.[1-5] We get from the Equation number (7) and (9) and their hybrid constant (A, B, a, b),

$C_p^0 = A+B$, (8)

$C_t^0 = 0$ (9)

$k_{21} = (Ab+Ba)/(A+B)$ (10)

$k_{12} = AB(a-b)^2/(A+B)(Ab+Ba)$ (11)

$k = ab(A+B)/(Ab+Ba)$ (12)

$T = AB(a-b)/(Ab+Ba)$ (13)

By solving the Equations (10), (11), and (12); 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

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 obviously obtained a non-linear curve rather than a straight line. Hence, the biexponential curve represents the distribution phase as well as elimination phase Figure 1.

Let the intrapolated data $c_1$, $c_2$, $c_3$ and $c_8$, $c_9$, $c_{10}$ lie in the distribution phase curve and elimination phase curve, respectively, of the biexponential curve.

According to biexponential distribution in plasma compartment, the initial distribution phase ($Ae^{-at}$) is more rapid than the elimination phase ($Be^{-bt}$).[6-11] Hence, it is considered with the increasing of time distribution phase slows down and elimination phase proceeds rapidly and $Ae^{-at}$ approaches to zero, $Be^{-bt}$ has a finite value.

Hence, it is obtained from the Equation (9)

Or, $C_p(t) = Be^{-bt}$.

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 $b_1$, $B_1$ can be easily determined from elimination phase data ($c_8$, $c_9$, $c_{10}$) and ($t_8$, $t_9$, $t_9$)

According to the Equation (i), $b = \{\ln(c_8) - \ln(c_9)\}/(t_9 - t_8)$ and $B = c_8/e^{-bt}{}_8$,

And the elimination half-life of the drug, $t_{1/2} = 0.693/b$.

In the distribution phase, the drug is also eliminated concurrently. Hence, we must take into consideration the eliminated fraction of the plasma drug concentration to determine the distribution

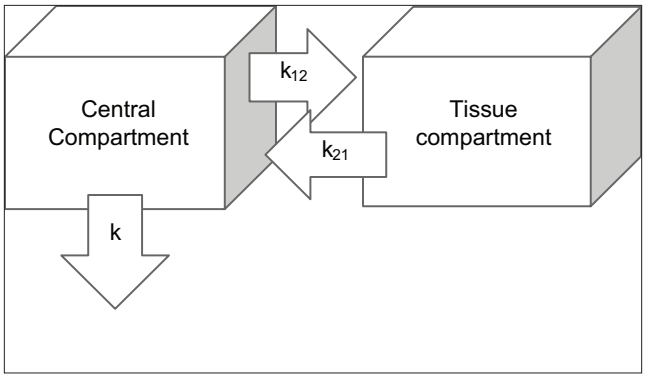


**Figure 1:** Two compartment open model

phase hybrid constants a, A. Hence, the eliminated fraction can be determined by, $c'_p = Be^{-bt}$,
Where, $c'_p$ is obtained from the distribution phase data ($c_1$, $c_2$, $c_3$). 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 is $c'_1$, $c'_2$, $c'_3$.
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, $C''_p(t) = Ae^{-at}$;
where, $C''_p(t) = C_p(t) - C'_p(t)$ is the residual plasma drug concentration
Let the residual plasma drug concentration is $c''_1$, $c''_2$, $c''_3$ with respect to eliminated fraction of drug from plasma $c'_1$, $c'_2$, $c'_3$
By taking the natural logarithm, it is obtained, $\ln(c''_p) = \ln(A) - at$ (ii)
According to equation, $a = \{\ln(c''_1) - \ln(c''_2)\}/(t_2 - t_1)$ and $A = c''_2/e^{-at_2}$

## RESULTS

Hence, all the pharmacokinetic factors as well as the drug concentration in plasma as well as tissue can be evaluated at any time.

## CONCLUSION

It is obvious that we can estimate the fate of a drug following open two compartment model at any time and predict the biological half-life of the drug and drug remained in peripheral compartment at any time.

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