Mathematical Treatment of Linear Mammillary Models Using Inverse Laplace Transforms

Keyphrases □ Mammillary models, linear—mathematics, inverse Laplace transforms □ Laplace transforms—inverse, in mathematical treatment of linear mammillary models □ Mathematics—inverse Laplace transforms in linear mammillary models

To the Editor:

In discussing linear mammillary models, Benet (1) used Laplace transform methods to solve the differential equations describing the compartmental exchanges of drug. Several investigators (2–5) described this method and gave it broader application and understanding relative to this type of pharmacokinetic modeling. However, none of these authors indicated a mathematical correction in the use of the Laplace transform to derive Eqs. 12 and 23 (1). In this article, we attempt to identify previous mathematical oversights and to offer a corrected derivation of the equations describing this model.

Equation 12 (1):

$$a_{s,1} = \frac{k^0(s + E_2)(s + E_3)(1 - e^{-bs})}{s(s + \alpha)(s + \beta)(s + \gamma)} \quad \text{(Eq. 1)}$$

is the Laplace transform for the amount of drug in the central compartment, Compartment 1, in a three-compartment model for an intravenous infusion over the time interval $0 \leq t \leq b$. The given equation is correct but, in determining the inverse Laplace transform of $a_{s,1}$, the numerator $k^0(s + E_2)(s + E_3)(1 - e^{-bs})$ has been misinterpreted as a polynomial in the variable s and, therefore, the General Partial Fraction Theorem has been misapplied. The presence of the factor $(1 - e^{-bs})$ destroys the polynomial character of the numerator, so neither the General Partial Fraction Theorem nor the Heaviside expansion immediately pertains (6).

The following modifications should be made:

$$a_{s,1} = \frac{k^0(s + E_2)(s + E_3)}{s(s + \alpha)(s + \beta)(s + \gamma)} - \frac{k^0(s + E_2)(s + E_3)}{s(s + \alpha)(s + \beta)(s + \gamma)} e^{-bs} \quad \text{(Eq. 2)}$$

The first term in this difference is the quotient of two polynomials, so the Heaviside expansion applies as follows:

$$L^{-1}\left\{\frac{k^0(s + E_2)(s + E_3)}{s(s + \alpha)(s + \beta)(s + \gamma)}\right\} = \frac{k^0(E_2)(E_3)}{\alpha\beta\gamma} + \frac{k^0(E_2 - \alpha)(E_3 - \alpha)}{-\alpha(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t} + \frac{k^0(E_2 - \beta)(E_3 - \beta)}{-\beta(\alpha - \beta)(\gamma - \beta)} e^{-\beta t} + \frac{k^0(E_2 - \gamma)(E_3 - \gamma)}{-\gamma(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t} \quad \text{(Eq. 3)}$$

To compute the inverse Laplace transform of the second term, a shift theorem should be used. Let $H(t - b)$ be a function defined by the expression

$$H(t - b) = \begin{cases} 0 & t < b \\ 1 & t > b \end{cases} \quad \text{(Eq. 4)}$$

This function is usually called the unit-step function or the Heaviside function (7). With $H(t - b)$, the needed shift theorem is easily stated. Let $b > 0$ and let the Laplace transforms of $F(t)$, $L\{F(t)\}$, exist. Then:

$$L\{F(t - b)H(t - b)\} = e^{-bs}L\{F(t)\} \quad \text{(Eq. 5)}$$

By applying this theorem under the assumption that:

$$F(t) = L^{-1}\left\{\frac{k^0(s + E_2)(s + E_3)}{s(s + \alpha)(s + \beta)(s + \gamma)}\right\} \quad \text{(Eq. 6)}$$

it is found that:

$$L^{-1}\left\{\frac{k^0(s + E_2)(s + E_3)}{s(s + \alpha)(s + \beta)(s + \gamma)} e^{-bs}\right\} = \left\{\frac{k^0E_2E_3}{\alpha\beta\gamma} + \frac{k^0(E_2 - \alpha)(E_3 - \alpha)}{-\alpha(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha(t-b)} + \frac{k^0(E_2 - \beta)(E_3 - \beta)}{-\beta(\alpha - \beta)(\gamma - \beta)} e^{-\beta(t-b)} + \frac{k^0(E_2 - \gamma)(E_3 - \gamma)}{-\gamma(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma(t-b)}\right\} H(t - b) \quad \text{(Eq. 7)}$$

When Eqs. 3 and 7 are combined, the solution becomes:

$$a_1 = k^0\left[\frac{E_2E_3}{\alpha\beta\gamma} - \frac{(E_2 - \alpha)(E_3 - \alpha)}{\alpha(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t} - \frac{(E_2 - \beta)(E_3 - \beta)}{\beta(\alpha - \beta)(\gamma - \beta)} e^{-\beta t} - \frac{(E_2 - \gamma)(E_3 - \gamma)}{\gamma(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t}\right] \quad \text{(Eq. 8)}$$

in the time interval $0 \leq t \leq b$ and:

$$a_1 = k^0\left[\frac{(E_2 - \alpha)(E_3 - \alpha)(e^{\alpha b} - 1)}{\alpha(\beta - \alpha)(\gamma - \alpha)} e^{-\alpha t} + \frac{(E_2 - \beta)(E_3 - \beta)(e^{\beta b} - 1)}{\beta(\alpha - \beta)(\gamma - \beta)} e^{-\beta t} + \frac{(E_2 - \gamma)(E_3 - \gamma)(e^{\gamma b} - 1)}{\gamma(\alpha - \gamma)(\beta - \gamma)} e^{-\gamma t}\right] \quad \text{(Eq. 9)}$$

in the time interval $t > b$. This solution coincides exactly with that of Benet (1) for $t > b$ and gives a more explicit solution for $0 \leq t \leq b$. It is a fact that if the constant b is allowed to vary while infusion continues, *i.e.*, $b = t$ in Ref. 1, one can simplify Benet's solution to the one proposed. However, changing constants to variables in the middle of a derivation confuses the reader and the simplification requires very tedious calculations. The proposed approach is more direct and leaves b as a fixed constant in the model.

With Eq. 23 (1):

$$a_{s,3} = \frac{k_{13}k^0(s + E_2)(1 - e^{-bs})}{s^2(s + \alpha)(s + \beta)} \quad \text{(Eq. 10)}$$

Benet wished to demonstrate how to handle a partial fraction decomposition in which the denominator has a repeated root. However, the numerator is misread as a polynomial in s. The term $a_{s,3}$ may be written as follows:

$$a_{s,3} = k_{13}k^0\left\{\frac{s + E_2}{s^2(s + \alpha)(s + \beta)} - \frac{(s + E_2)e^{-bs}}{s^2(s + \alpha)(s + \beta)}\right\} \quad \text{(Eq. 11)}$$

Then, by using the expansion described by Benet in the Appendix (1) and the shift theorem quoted above, the following expression is obtained from Eq. 11:

$$L^{-1}\{a_{s,3}\} = k_{13}k^0\left[\frac{1 - (\alpha + \beta)E_2}{\alpha\beta} + \frac{tE_2}{\alpha\beta} + \frac{(E_2 - \alpha)e^{-\alpha t}}{\alpha^2(\beta - \alpha)} + \frac{(E_2 - \beta)}{\beta^2(\alpha - \beta)} e^{-\beta t}\right] \quad \text{(Eq. 12)}$$

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for $0 \leq t \leq b$ and:

$$L^{-1}\{a_{s,3}\} = k_{13}k^0\left[\frac{E_2 b}{\alpha\beta} + \frac{(E_2-\alpha)(1-e^{\alpha b})e^{-\alpha t}}{\alpha^2(\beta-\alpha)} + \frac{(E_2-\beta)(1-e^{\beta b})e^{-\beta t}}{\beta^2(\alpha-\beta)}\right] \quad \text{(Eq. 13)}$$

for $t > b$. Equation 13 coincides with Eq. 24 (1), which is valid for the model only after infusion has ceased. Equation 12 gives a very explicit form of the solution during the infusion time.

It is hoped that the corrections made in this article can contribute to the broader application and understanding of the method proposed by Benet.

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Mathematical Treatment of Linear Mammillary Models Using Inverse Laplace Transforms: A Reply

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To the Editor:

The impetus for preparing my 1972 paper on the general treatment of linear mammillary models as used in pharmacokinetics (1) was a sense of frustration with the pages of mathematical derivation included as part of each pharmacokinetic paper that appeared in print up to that time. As I stated in the introduction (1): "This paper intends to present some very simplified general treatments which will allow workers to derive equations for any linear mammillary compartment model with any first- or zero-order input process." I believed then, as I believe now, that pharmacokinetic compartment models are useful only as a convenient means to describe and predict the time course of measurable body fluid compartments such as plasma, blood, and urine following single and multiple doses. I did not consider the possibility of input into a peripheral compartment or the general derivation for such a treatment, as was described by Vaughan and Trainor (2), since I believe this use of compartment models is inappropriate, *i.e.*, defining one compartment in the model as specifically describing an organ in the body such as the liver. Such a combination of compartment and perfusion models requires exponential terms that are not needed to fit the minimal compartment model adequately and leads to difficulties in interpreting "absorption" rate constants for such a system.

Haborak *et al.* (3) questioned the solution of two equations in my earlier paper, stating: "The presence of the factor $(1 - e^{-bs})$ destroys the polynomial character of the numerator, so neither the General Partial Fraction Theorem nor the Heaviside expansion immediately pertains." They are correct. However, the correct solution is also obtained using the one-step method that I proposed (1, 4). Apparently, the restriction concerning the polynomial character of the numerator may be relaxed when exponential functions appear in the numerator due to the inclusion of a zero-order input function. Since I am no mathematician, I shall leave the proof of this exception to others. However, I have tested the one-step method and found that it gives the correct equations for the usual multicompartment pharmacokinetic models with zero-order input into the central or peripheral compartments.

The authors of the preceding article (3) were most disturbed by the fact that I proposed the use of a single equation to describe the time course of drug in the central compartment during infusion *and* when infusion has ceased. Although I did explain, following Eq. 13 (1), that this approach was equivalent to using two independent variables, t = clock time and b = infusion time, Haborak *et al.* (3) stated that "changing constants to variables in the middle of a derivation confuses the reader . . .." I must admit that this point has led to questions by a number of readers over the years. Perhaps the preceding note and this reply will help readers to understand the appropriate use of Eqs. 13 and 24 in the 1972 paper (1).

Haborak *et al.* (3) also stated that my use of a single equation "requires very tedious calculations." This statement I do not understand; it certainly would be quicker to calculate A_1 values in Eq. 13 on any programmable calculator using a single equation with two inputs during the infusion phase than it would be using two different equations. But "calculation" is not the important functional use for Eq. 13. In 1972, I was concerned that investigators were fitting data from the postinfusion phase separately from the infusion phase. This procedure is inappropriate, as I stated previously (1). In 1972, many of the computer programs used to fit pharmacokinetic data, particularly the BMD series (5), only allowed the investigator to fit one function at a time. However, I stated then (1) that: "All the least-squares nonlinear fitting programs usually utilized in pharmacokinetic treatments have the ability to fit data to Eq. 13. . . ."

In conclusion, the previous article (3) points out the detailed solution for the Laplace derivation when an exponential operator term appears in the numerator of the

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