ANALYSIS OF METABOLITE FORMATION PHARMACOKINETICS AFTER INTRAVENOUS AND ORAL ADMINISTRATION OF THE PARENT DRUG USING INVERSE LAPLACE TRANSFORMATION

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ABSTRACT:
Models describing the plasma concentration-time curves of generated metabolite after iv and oral drug administration are presented. Utilizing numerical inverse Laplace transformation, the method can readily be used for parameter estimation and model simulation in conjunction with appropriate curve-fitting software. The approach is not limited to compartment modeling and can be applied to any linear pharmacokinetic system exhibiting hepatic and renal elimination of the parent drug. The model is formulated for single and multiple dosing of the precursor, including bolus doses and/or infusions for iv administration and sustained-release dosage forms for oral administration.

To date, two different methods have been used for modeling of metabolite kinetics, i.e., the mathematical analysis of concentration-time curves of a parent drug and the generated metabolite: classical compartmental models and so-called model independent approaches, which are not restricted to the assumption of well-mixed compartments and simple first-order transfer processes. One reason why non-compartmental methods are applied relatively seldomly to the prediction (analysis) of concentration-time curves of a formed metabolite is the need to apply convolution (deconvolution) methods. Although the discussion of deconvolution methods is out of the scope of this paper, it should be noted that these methods have practical limitations (instability in the case of noisy data and no direct estimation of metabolite parameters). We propose here a simple and practicable method that is based on a general model of metabolite kinetics after iv and oral administration of the parent drug (Weiss, 1988). This approach, which was originally used to estimate curve moments—i.e., pharmacokinetic parameters that are dependent on the AUCs or mean residence times—is now extended to the analysis of the time-course of metabolite concentration. Since the dispositions of drug and metabolite can be regarded as consecutive subsystems, modeling is greatly simplified in the Laplace domain. While the model equations can be readily formulated, the crucial point for the application in practice is the availability of methods of the numerical inverse Laplace transformation to obtain \(C(t)\) from \(\hat{C}(s)\), the corresponding model in the Laplace domain.

In recent years, appropriate curve-fitting software became available in which such numerical inversion methods are implemented: for example, SCIENTIST (MicroMath Scientific Software, Salt Lake City, UT) for DOS, and MINIM (Purves, 1995) for Macintosh computers. We have also applied this method in combination with the widely used ADAPT II program. For the evaluation of metabolite concentration-time curve after oral administration of the parent drug, a flexible oral input model has been utilized (Weiss, 1996).

Materials and Methods

Pharmacokinetic Model. As shown in fig. 1, the complete model for oral administration of drug and iv administration of precursor and preformed...
metabolite can be decomposed into subsystems describing drug input and the disposition processes of drug and metabolite, respectively.

Input models: drug dosing. The input function in the Laplace domain for administration of a bolus dose $D_n$ (at $t = 0$)

$$\tilde{I}_{p,\text{bolus}}(s) = \tilde{I}_{p,\text{bolus}}(s) = D_n$$

(1)

and infusion with rate $k_o$ over a time period $T$ (e.g. Wagner, 1975),

$$\tilde{I}_{p,\text{dose}}(s) = \tilde{I}_{p,\text{dose}}(s) = \frac{k_o}{s}(1 - e^{-T})$$

(2)

have to be added in the case of a dosing schedule consisting of a simultaneous administration of a bolus dose and short-term infusion [$\tilde{I}_p(s) = \tilde{I}_{p,\text{bolus}}(s) + \tilde{I}_{p,\text{dose}}(s)$]. For multiple dosing ($N$ bolus doses or infusions with a dosing interval $\tau$), these equations have to be substituted into eq. 3, which describes the multiple input function $\tilde{I}_{p,\text{bolus}}(s)$ in terms of the corresponding single input function $\tilde{I}_{p,\text{bolus}}(s)$ (e.g. Weiss and Förster, 1979)

$$\tilde{I}_{p,\text{bolus}}(s) = \tilde{I}_{p,\text{bolus}}(s) \sum_{n=1}^{N} e^{-\frac{n-1}{\tau}} \tilde{I}_{p,\text{bolus}}(s)$$

(3)

Note that for oral drug administration only eqs. 1 and 3 with $\tilde{I}_{p,\text{bolus}}(s) = \tilde{I}_{p,\text{bolus}}(s)$ are of interest.

Disposition models. Disposition curves of the drug and the preformed metabolite are described by a sum of exponentials

$$C_m(t) = \sum_{i=1}^{n} A_i e^{-\lambda_i t}$$

(4)

where $C_m(t)$ denotes the concentration-time profile after an intravenous dose $D_n$ and the $2n$ parameters $A_i$ and $\lambda_i$, which define this empirical function, can be estimated by nonlinear regression (mostly $2 \leq n \leq 4$). The corresponding unit impulse response of the system is given by

$$\tilde{\Psi}_p(s) = \frac{C_p(t)}{D_n} = \sum_{i=1}^{n} A_i e^{-\lambda_i s}$$

(5)

where $\lambda_i = A_i/D_n$. The Laplace transformation of eq. 5 used to characterize the behavior of the subsystems (fig. 1) is then given by

$$\tilde{\Psi}_p(s) = \sum_{i=1}^{np} \alpha_{p,i} s + \lambda_{p,i}$$

(6)

for the precursor and by

$$\tilde{\Psi}_m(s) = \sum_{i=1}^{nm} \alpha_{m,i} s + \lambda_{m,i}$$

(7)

for the metabolite.

Concentration-Time Profiles of the Drug. The plasma concentration-time curve $\tilde{C}_p(s)$ of the drug after an input or dosing function, $\tilde{I}_p(s)$ can be written as

$$\tilde{C}_p(s) = \tilde{I}_p(s) \tilde{\Psi}_p(s)$$

(8)

For iv administration, the input function $\tilde{I}_{p,\text{bolus}}(s)$ is identical to the dosing function (eqs. 1, 2, or 3),

$$\tilde{C}_{p,\text{bolus}}(s) = \tilde{I}_{p,\text{bolus}}(s) \tilde{\Psi}_p(s)$$

(9)

whereas in the case of oral administration

$$\tilde{C}_{p,\text{oral}}(s) = \tilde{I}_{p,\text{oral}}(s) \tilde{\Psi}_p(s)$$

(10)

the processes of drug absorption and primary liver passage have to be modeled to determine $\tilde{I}_{p,\text{oral}}(s)$. For an input function $\tilde{\Psi}_A(s)$ describing the dynamics of the input process (dissolution, absorption, and liver transit time), we have

$$\tilde{I}_{p,\text{oral}}(s) = D_A F \tilde{\Psi}_A(s)$$

(11)

where $F$ denotes bioavailability. As shown recently (Weiss, 1996), the inverse Gaussian density

$$\tilde{\Psi}_A(s) = \frac{1}{CV_A^{1/2}} \left( 1 + \frac{1}{2MAT CV_A^2} s^2 \right)^{-1/2}$$

(12)

with mean input (or absorption) time $MAT$ and the normalized variance of the distribution $CV_A^2$ represents a flexible input function. It follows from eqs. 10, 6, and 12 that the concentration-time curve of the drug after an oral dose is given by (Weiss, 1996)

$$\tilde{C}_{p,\text{oral}}(s) = D_A F \exp \left( \frac{1}{CV_A^{1/2}} \left( 1 + \frac{1}{2MAT CV_A^2} s^2 \right)^{1/2} \right) \sum_{i=1}^{np} \frac{\alpha_{p,i}}{s + \lambda_{p,i}}$$

(13)

where the bioavailability of the drug $F = F_d F_{H \rightarrow p}$ is the product of the fraction absorbed $F_d$ and the hepatic first-pass availability $F_{p \rightarrow p}$ (extraction ratio across the liver, $E_{H \rightarrow p} = 1 - F_{H \rightarrow p}$). Note that a simple first-order input process

$$\tilde{\Psi}_A(s) = \frac{k_a}{s + k_a}$$

(14)

with mean absorption time $MAT = 1/k_a$, fails to describe the dissolution/absorption process of retard formulations (Weiss, 1996); however, if this one parameter model should prove sufficient in special cases, it could be used instead of eq. 12.

Concentration-Time Profiles of the Formed Metabolite. For iv administration, the time course of $C_m(t)$ determines the input rate $\tilde{I}_{m,\text{oral}}(s)$ of the metabolite ($m$) generated from the parent drug ($p$):

$$\tilde{I}_{m,\text{oral}}(s) = F_m CL_p \tilde{\Psi}_{m,\text{oral}}(s) \tilde{\Psi}_{p,\text{oral}}(s)$$

(15)

where $CL_p$ is the total clearance of the drug, $F_m$ denotes the fraction of drug $p$ metabolized to the primary metabolite $m$ and $\tilde{\Psi}_{m,\text{oral}}(s)$ is the liver transit time density corresponding to the formation of $m$ from drug $p$. According to the principle of parsimony, we have selected the well-stirred model as the simplest pharmacokinetic liver model, where the hepatic transit time function

$$\tilde{\Psi}_{m,\text{oral}}(s) = \frac{\lambda_m}{s + \lambda_m}$$

(16)

is determined by a single parameter $\lambda_m$ and the mean transit time across the liver is given by $MTT_H = 1/\lambda_m$. Substituting eqs. 16 and 9 into eq. 15, then the latter and eq. 7 into eq. 9, one obtains the equation describing the time course of metabolite concentration generated after iv administration ($\tilde{I}_{p,\text{oral}}$ according to eqs. 1 through 3) of the precursor drug:

$$\tilde{C}_{m,\text{oral}}(s) = \tilde{I}_{p,\text{oral}} F_m CL_p \frac{\lambda_m}{s + \lambda_m} \sum_{i=1}^{np} \frac{\alpha_{p,i}}{s + \lambda_{p,i}} \sum_{i=1}^{nm} \frac{\alpha_{m,i}}{s + \lambda_{m,i}}$$

(17)

If we denote by $h_{m,\text{oral}}$ and $f_e$ the fraction of hepatic clearance $CL_{H \rightarrow p}$ that forms the metabolite $m$ and the fraction of drug excreted unchanged into urine, respectively, we have

$$h_{m,\text{oral}} = F_m f_e (1 - f_e)$$

(18)

since the following equation holds: $h_{m,\text{oral}} CL_{H \rightarrow p} = h_{m,\text{oral}} (1 - f_e) CL_p = F_m CL_p$, In the case of oral administration additionally to the hepatic metabolism formation $\tilde{I}_{m,\text{oral}}(s)$ from input concentration $\tilde{C}_{m,\text{oral}}(s)$ (eqs. 13 and 15), the first-pass metabolism described by $\tilde{I}_{m,\text{oral}}(s)$ (cf. fig. 1) must be considered,

$$\tilde{I}_{m,\text{oral}}(s) = D_A F_A (1 - F_{H \rightarrow p}) h_{m,\text{oral}} \tilde{\Psi}_A(s) \tilde{\Psi}_{H,\text{oral}}(s),$$

(19)
and the total metabolite input function is given by

\[ \hat{I}_{\text{mp,}\omega}(s) = D_{\omega} F_A \hat{\Psi}_{\text{mp,}\omega}(s)(1 - F_{\text{mp}}) \hat{\Psi}_{\omega}(s) + F_{\text{mp}} CL_p \hat{\Psi}_{\text{mp,}\omega}(s) \hat{\chi}_{\text{mp,}\omega}(s) \]  

(20)

Finally, after substituting eqs. 20, 16, and 18 into eq. 10, we get

\[ \hat{C}_{\text{mp,}\omega}(s) = D_{\omega} F_A \exp \left[ \frac{1}{CV_A^2} \left( \frac{MAT}{CV_A^2} s + \frac{1}{2MAT CV_A^2} \right)^{1/2} \right] \]  

\[ \times \left( \frac{1 - F_{\text{mp}}}{1 - f_{\text{fr}}} + F_{\text{mp}} CL_p \frac{\lambda_H}{s + \lambda_{\text{mp}}} \sum_{i=1}^{\eta} \alpha_{p,i} \right) \]  

\[ \times \left( \sum_{i=1}^{\eta} \frac{\alpha_{m,i}}{s + \lambda_{m,i}} \right)^{\text{max}} \]  

(21)

Note that for multiple dosing, \( D_{\omega} \) has to be substituted by \( D_{\omega} \sum_{i=1}^{\text{max}} e^{-(\text{max}-1)i\tau} \) (cf. eq. 3).

Results and Discussion

Model Simulation. The effect of different dosing schedules on the time course of the parent drug and the formed metabolite has been simulated according to eqs. 9, 13, 17, and 21, respectively, using the software package SCIENTIST (fig. 2). The underlying model parameters of a high-clearance drug (80% hepatic extraction) with a fraction metabolized to the primary metabolite of 10% are characteristic for the metabolism of morphine to morphine-6-glucuronide in humans (Hasselström and Säwe, 1993; Lőtsch et al., 1998). The dosing interval for the four intravenous bolus doses is 6 hr. For oral administration, the response to a slow-release formulation (MAT = 5 hr, \( CV_H^2 = 0.8 \)) is compared with that of a normal tablet (MAT = 1 hr, \( CV_H^2 = 0.8 \)), assuming that the dose is divided into four doses administered in intervals of 6 hr, as in the case of intravenous administration.

Data Analysis. Analogously to the situation in the analysis of pharmacokinetic systems after oral administration, in which intravenous data are necessary to identify the system, a complete identification of the metabolite formation kinetics (i.e., estimation of parameters in eq. 21) is only possible if disposition data of the preformed metabolite are available. Data analysis starts with fitting of the \( C_{p,\text{iv}}(t) \) and \( C_{m,\text{iv}}(t) \) curves observed after iv administration of precursor \( (p) \) and metabolite \( (m) \), respectively. In this case, the disposition curves in the time domain (eq. 4) can be used for parameter estimation, or for infusion with rate \( k_0 \) over a time period \( T \).

\[ C(t) = k_0 \sum_{i=1}^{\eta} \left( \frac{e^{\theta}\frac{\tau}{T}}{1 - \frac{\theta}{T}} \right) e^{-\lambda_H t} \]  

(22)

where \( \theta = t, \) for \( t < T, \) or \( \theta = T, \) for \( t \geq T. \)

The number of exponential terms \( (np) \) and \( (nm) \) can be determined using a model selection criterion (e.g., the MSC criterion of SCIENTIST, which is a modified Akaike information criterion). The estimated disposition parameters of parent drug \( (\alpha_{p,i} \) and \( \lambda_{p,i} \)), \( i = 1..np \)) and metabolite \( (\alpha_{m,i} \) and \( \lambda_{m,i} \)), \( i = 1..nm \) \) and the derived pharmacokinetic parameter, \( CL_p = 1/\sum_{i=1}^{\eta} \alpha_{p,i}/\lambda_{p,i}, \) are then substituted into eq. 17 in the case of iv drug administration. These parameters are held fixed in the fitting of the formed metabolite \( [C_{mp,\text{iv},t}(t)] \) data to estimate \( \lambda_H \) (= \( \text{MTT}_p \)) and \( F_{\text{mp}}. \) Since numerical inverse Laplace transformation \( C(t) = L^{-1}[\hat{C}(s)] \) is part of the fitting procedure, all model equations can be used as given in the Laplace domain. For oral administration, the concentration-time curve of the precursor \( (C_{p,\omega}(t)) \) is not available in the time domain, and eq. 13 has to be fitted to the data to estimate \( F, MAT \) and \( CV_H^2 \) (Weiss, 1996). Again, the estimated parameters are held fixed in fitting eq. 21 to the curve of the metabolite generated after oral administration of the drug. (The only parameter that remains to be estimated in this fit is \( F_{\text{mp}} \), since \( F_A = F/F_{\text{mp}} \).)

Conclusion. In this paper, we presented an approach to parameter estimation and model simulation in metabolite kinetics formulated in terms of Laplace transforms. Numerical inversion of the equations by a curve-fitting software makes the method user-friendly. The SCIENTIST program files of the described solutions can be found in the Appendix. Despite some simplifying assumptions, the model is more general than previous concepts (Karol and Goodrich, 1988; Chan and Gibaldi, 1990; Nigrovic and Banoub, 1992). The basic structure of the noncompartmental model (fig. 1) was originally used in applying statistical moment theory to metabolite kinetics (Weiss, 1988). Apart from the intrinsic disposition parameters of the metabolite, its formation kinetics after intravenous administration of the parent drug are described by only two parameters, the fraction of drug metabolized to the metabolite and the time constant of the hepatic formation process, i.e., the mean transit time across the liver for drug input and metabolite output. The evaluation of metabolite kinetics after oral administration of the precursor is based on a flexible input function that allows an application to immediate and controlled release tablets (Weiss, 1996). Note that in the case of first-pass metabolism the liver transit time is part of MAT, the input time of the precursor. As shown earlier on the basis of the AUCs or steady-state concentrations (Weiss, 1990), the assessment of metabolite kinetics enables us to distinguish between the fraction absorbed \( (F_A) \)
and first-pass extraction \((1 - F_{H,p})\) of the drug as determinants of bioavailability. The utilization of the present approach can be useful in the design and pharmacokinetic analysis of novel controlled-release dosage forms. The flexibility of the input mode (multiple dosing) might also be of interest for toxicokinetic applications. Part of this theory has been applied successfully to analyze metabolite kinetics after iv administration of morphine to healthy volunteers (Lötsch et al., 1998).

**References**


**Appendix**

**SCIENTIST program source listings for the case of two-exponential disposition of the precursor and preformed metabolite \((np = nm = 2)\) following a bolus dose \(D_{iv}\).**

// Equation 5
IndVars: T
DepVars: Civ
Params: Div, a1, a2, 11, 12
Civ = Div*(a1*exp(-11*T) + a2*exp(-12*T))
// Div constant
***

**C(t) of drug (precursor) after an oral dose \(D_{or}\).**

// Equation 13
IndVars: T
LaplaceVar: s
DepVars: Co
Params: Dor, F, CVs, MAT, 1h, a1, a2, 11, 12
fp = a1/(s+1)+a2/(s+12)
m = 2*MAT/CVs
n = 1/(2*MAT*CVs)
CoL = Dor*F*exp(-sqrt(m*(s+n))+1/CVs)
Co = LAPLACEINVERSE(T, CoL, s)
// Dor constant
// a1, a2, 11, 12 fixed parameters if estimated in eq. 5
***

**C(t) of metabolite after an iv dose of precursor \(D_{iv}\).**

// Equation 17
IndVars: T
LaplaceVar: s
DepVars: Cm
Params: Div, Fmp, CL, 1h, a1, a2, 11, 12, am1, am2, lm1, lm2
fp = a1/(s+1)+a2/(s+12)
fm = am1/(s+lm1)+am2/(s+lm2)
CmL = Div*Fmp*CL*(lh/(s+lh))*fp*fm
Cm = LAPLACEINVERSE(T, CmL, s)
// Div constant
// a1, a2, 11, 12, am1, am2, lm1, lm2, CL fixed parameters
***

**C(t) of metabolite after an oral dose of precursor \(D_{or}\).**

// Equation 21
IndVars: T
LaplaceVar: s
DepVars: Cmo
Params: Dor, F, Fh, Fe, Fmp, CVs, MAT, CL, 1h, a1, a2, 11, 12, am1, am2, lm1, lm2
fp = a1/(s+1)+a2/(s+12)
fm = am1/(s+lm1)+am2/(s+lm2)
x = exp(-sqrt(m*(s+n))+1/CVs)
CmoL = Dor*(F/Fh)*Fmp*x*(1-Fh)/(1-Fe) + Fh*CL*(1h/(s+lh))*fp*fm
Cmo = LAPLACEINVERSE(T, CmoL, s)
// Dor constant
// a1, a2, 11, 12, am1, am2, lm1, lm2, CL, 1h, Fmp, F, CVs, MAT fixed parameters
***