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A pharmacokinetic model for analysis of drug disposition profiles undergoing enterohepatic circulation

Toshihiro Wajima, Yoshitaka Yano and Takayoshi Oguma

Abstract

A new and simple pharmacokinetic model that can explain enterohepatic circulation profiles for both single and repeated dosing was developed, and its applicability and usefulness were assessed by an actual published data set and simulation study. The model is basically a conventional compartment model, and the transfer rate from the bile compartment to the central compartment is assumed to change periodically, with the sine function being used to describe this periodical change. Using this model, the effect of the parameter values on plasma time-course profiles was examined by simulation, and the applicability of the model was tested by curve fitting to obtain the parameter estimates using an actual published data set. These studies confirmed that our model can simulate the periodical increase of the concentration due to re-absorption. By averaging the sine function in the transfer rate from the bile compartment to the central compartment, a smoothed time-course profile in the elimination phase that is independent of the enterohepatic cycle can be obtained. Also, the apparent half-life in the elimination phase can be estimated, which is useful especially for evaluating drug accumulation during repeated dosing. It was suggested that the present model can be used to evaluate the drug disposition profile with enterohepatic circulation. The effects of sampling points and sampling time on parameter estimation are also discussed.

Introduction

The enterohepatic circulation of a drug is an important factor for evaluating its efficacy via pharmacokinetic and pharmacodynamic analyses. Enterohepatic circulation is a unique phenomenon because a drug molecule that has gone out of the systemic circulation returns and contributes again to the pharmacokinetic/pharmacodynamic (PK/PD) profile. Several pharmacokinetic models have been tried to explain the enterohepatic circulation of a drug; the most popular are compartment models with a lag time (sometimes called gap time), from bile compartment to plasma compartment (Dahlstrom & Paalzow 1978; Pedersen & Miller 1980a, b; Steimer et al 1982; Colburn 1984; Miller 1984; Shepard et al 1985, 1989; Plusquellec & Houin 1992, 1995; Hoglund & Ohlin 1993; Khalil et al 1993; Plusquellec et al 1998; Funaki 1999). To simulate the secondary peaks in a plasma concentration profile due to enterohepatic circulation, the recirculatory concept, in which enterohepatic circulation is regarded as a recirculation process of drug molecules between the bile and the plasma compartments, has also been proposed (Yamaoka et al 1990; Fukuyama et al 1994; Yasui et al 1994, 1996). However, these methods have only been used to explain the data in a single dosing study, and there have been few reports on pharmacokinetic models applied to data analysis in a repeated dosing study. Possible reasons for this limitation include the increase of the number of model parameters. For example, in compartment models with a lag time (gap time), the lag-time parameter would be required at each point of lag time (i.e. at the time re-absorption begins) and also at each dosing in the repeated schedule.

The purpose of this study is to develop a new and simple pharmacokinetic model that can explain the enterohepatic circulation profiles in both single and repeated dosing, and to assess the model by simulation study. The model is also examined in relation to

Developmental Research Laboratories, Shionogi & Co. Ltd, Sagisu 5-12-4, Fukushima-ku, Osaka 553-0002, Japan

Toshihiro Wajima, Yoshitaka Yano, Takayoshi Oguma

Correspondence: Y. Yano, Developmental Research Laboratories, Shionogi & Co. Ltd, Sagisu 5-12-4, Fukushima-ku, Osaka 553-0002, Japan. E-mail: yoshitaka.yano@shionogi.co.jp

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a statistical moment, AUC, and a useful approximation for evaluating the apparent half-life in a terminal phase is presented. Finally, a simulated data set is used to examine the effect of sampling points and sampling time on parameter estimation.

Theory

Our enterohepatic circulation model is based on the concept of the conventional compartment model, and any route of drug administration and any number of compartments are theoretically applicable. Here we present the details based on a conventional one-compartment model as an example. Figure 1 presents the scheme of the enterohepatic circulation model for the case of a one-compartment model with first-order absorption and absorption lag time.

In this model, compartment 1 is the central (plasma) compartment, compartment A is the intestinal compartment from which absorption takes place, and compartment B is the bile compartment that is related to enterohepatic circulation. A circulatory process between compartments 1 and B contains movement of drug molecules from the systemic circulation to the gastrointestinal tract via bile excretion and re-absorption into the systemic circulation. The transfer rate constant from compartment B to compartment 1 changes periodically, and the sine function is applied here to represent the periodical change as follows:

$$k_{B1} \times \sin\{2p/x\,(t+u)\} \tag{1}$$

where k_{B1} (h^{-1}) is the maximum transfer rate constant from compartment B to compartment 1, x is the period of the sine function (i.e. a cycle of enterohepatic circulation) and u gives the delayed time of the period from the first dosing time. When the value of equation 1 is negative, the transfer rate constant is assumed to be zero (i.e. no transfer occurs during this period). The parameters ka (h^{-1}), ke (h^{-1}) and k_{1B} (h^{-1}) are the absorption rate constant, the elimination rate constant and the transfer rate constant from compartment 1 to compartment B, respectively. All these processes are assumed to be of the first order. The irreversible transfer process in the re-absorption process is included in ke. Therefore the ratio $k_{1B}/(ke+k_{1b})$ indicates the fraction of re-absorbed drug throughout one cycle of the enterohepatic circulation. Lag time (T_{lag}) is assumed for the absorption process from compartment A. The apparent volume of distribution (distribution volume divided by the bioavailability) can be defined by the parameter V/F for compartment 1.

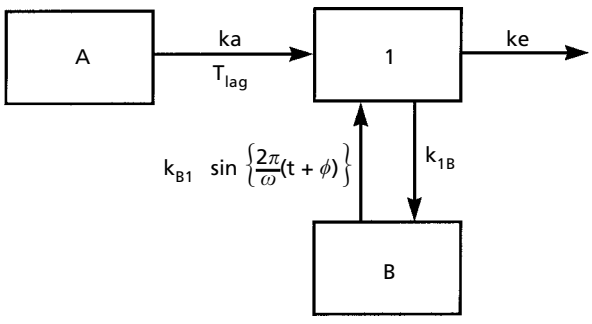

Figure 1 The enterohepatic circulation model.

Enterohepatic circulation begins with time delay x − u from the time of the first dosing. The circulation continues for x/2 h and then pauses for x/2 h, and it is assumed the same cycle is repeated every x h infinitely. Although the sine function is used in this report, other periodic functions may be used to represent the cycle. Here, we thought the sine function to be the simplest and the most convenient for pharmacokinetic data analysis. In the realistic situation, bile excretes into the small intestine rather than the blood circulation. However, to simplify the model and to minimize the number of the parameters, the drug of the bile compartment is assumed to transfer directly into the blood compartment in this model.

According to the model presented in Figure 1, the differential equations (mass-balance) in this model can be written as follows:

$$dC_1/dt = (-ke \cdot C_1 \cdot V - k_{1B} \cdot C_1 \cdot V + k_{B1} \cdot f(t) \cdot X_B + a \cdot X_A)/V \tag{2}$$

$$dX_B/dt = k_{1B} \cdot C_1 \cdot V - k_{B1} \cdot f(t) \cdot X_B \tag{3}$$

$$dX_A/dt = -a \cdot X_A \tag{4}$$

where $X_A = F \cdot Dose$ at $t = 0$

$$a = 0 \text{ when } t < T_{lag}, \quad a = ka \text{ when } t > T_{lag} \tag{5}$$

$$f(t) = \sin\{2p/x\,(t+u)\}; \quad \text{when } \sin\{2p/x\,(t+u)\} < 0, \quad f(t) = 0 \tag{6}$$

where C_1, X_A and X_B are the concentration of drug in compartment 1, the amount of drug in compartment A and the amount of drug in compartment B, respectively. Parameter V is the distribution volume of compartment 1 and a is the temporary parameter to describe an absorption rate constant.

Re-absorption of drug by enterohepatic circulation increases the area under the plasma concentration–time curve (AUC) and prolongs the elimination half-life. In the present model, AUC estimated for enterohepatic circulation (AUC_{EHC}) is

$$AUC_{EHC} = F \cdot Dose/(ke \cdot V) \tag{7}$$

and if no enterohepatic circulation is assumed to occur, (in this case k_{B1} is always equal to zero), AUC ($AUC_{non\text{-}EHC}$) is given by equation 8:

$$AUC_{non\text{-}EHC} = F \cdot Dose/\{(ke+k_{1B}) \cdot V\} \tag{8}$$

From equations 7 and 8, the AUC ratio due to the effect of enterohepatic circulation is given by equation 9:

$$AUC_{EHC}/AUC_{non\text{-}EHC} = (ke+k_{1B})/ke = 1+(k_{1B}/ke) \tag{9}$$

It is clear from equation 9 that the AUC increases k_{1B}/ke times due to enterohepatic circulation. Equations 7–9 are valid for any number of compartments. In the case of intravenous administration, F is 1 and equation 9 is still true.

We can apply the recirculatory concept (Yamaoka et al 1990) in the present model. The extraction ratio throughout the single-pass (one-cycle) process between compartment 1 and compartment B can be estimated by equation 10.

$$Ec = ke/(k_{1B}+ke) \quad (10)$$

Therefore the recovery ratio after the single-pass process is given by equation 11.

$$Fc = 1-Ec = k_{1B}/(k_{1B}+ke) \quad (11)$$

The recovery ratio for infinite recirculation (Tse et al 1982) is

$$F_{inf} = Fc+Fc^2+Fc^3+\cdots = Fc/(1-Fc) = k_{1B}/ke \quad (12)$$

and this ratio corresponds to the increase of the AUC value due to the influence of enterohepatic circulation in equation 9.

For a drug that shows enterohepatic circulation, the plasma concentration profiles change (wave) periodically and it is usually difficult to evaluate the elimination half-life. Based on the present model, the apparent elimination half-life can be easily estimated by averaging the periodic plasma concentration profiles. The averaged value of f(t) can be calculated by equation 13.

$$\bar{f} = \frac{1}{x}\int_0^{\frac{x}{2}} \sin\left\{\frac{2p}{x}t\right\} dt = \frac{1}{x}\frac{x}{p} = \frac{1}{p} \quad (13)$$

In equations 2–4, substitute f(t) as follows:

$$f(t) = 1/p \quad (14)$$

Next, assuming that the effect of the absorption phase on the elimination half-life is negligible, the apparent elimination half-life can be approximately obtained as follows:

$$b = \tfrac{1}{2}\{(k_{1B}+k_{B1}/p+ke) - \sqrt{(k_{1B}+k_{B1}/p+ke)^2-4\cdot k_{B1}/p\cdot ke}\} \quad (15)$$

$$t_{\frac{1}{2}}b = \ln 2/b \quad (16)$$

In the case of the two-compartment enterohepatic circulation model, one more mass-balance equation:

$$dX_2/dt = k_{12}\cdot C_1\cdot V - k_{21}\cdot X_2 \quad (17)$$

is considered and the term $-K_{12}\cdot C_1+K_{21}\cdot X_2/V$ is added to equation 2. In equation 17, K_{12} and K_{21} are first-order transfer rate constants between the central compartment and the peripheral compartment (compartment 2), and X_2 is the amount in the peripheral compartment. In this case, the model becomes a three-compartment model, and half-lives in the b- and c-phase in the conventional three-compartment model are applicable but a cubic equation must be solved. A numerical method such as the Newton–Raphson method is useful for this or an analytical method can be used. Details of the analytical solution are given in the Appendix.

Simulation and Curve Fitting

Our model is newly developed and should be useful to examine the effects of model parameters on plasma concentration profiles using simulation. In the following simulations (Figures 2 and 3), default values of each parameter are: dose = 100 mg, ka = 10 h^{-1}, ke = 0.1 h^{-1}, V/F = 100 L, k_{1B} = 0.1 h^{-1}, k_{B1} = 0.5 h^{-1}, x = 12 h, u = 6 h and T_{lag} = 1 h. Specific values used for the simulations are shown in the Figures. All simulation procedures were performed using the pharmacokinetic analysis program NONLIN (Metzler et al 1974) on a UNIX operating system with a FORTRAN compiler (Sun Pro). As it is difficult to analytically solve equations 2–6, the Runge–Kutta–Gill method (Press et al 1993) was used to obtain numerical solutions.

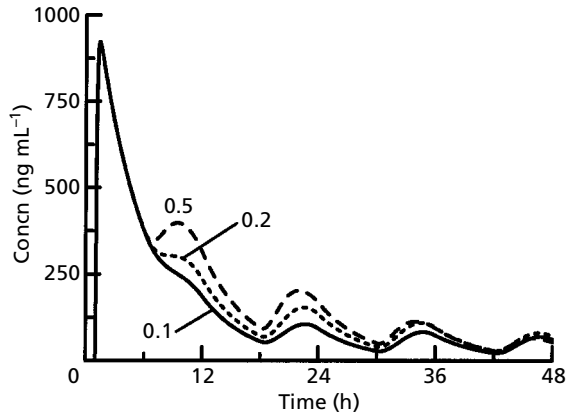

Figure 2 Effect of model parameters on plasma drug concentration profiles (k_{B1} = 0.1, 0.2, 0.5 h^{-1}).

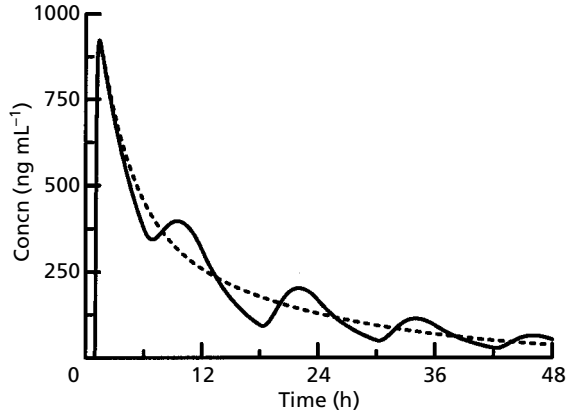

Figure 3 Example of averaged time-course plasma drug concentration profile. The solid curve is the true profile and the dotted curve is the averaged profile. All parameters are the default values.

As an example of curve fitting using the present enterohepatic circulation model, a data set from Gabrielsson & Weiner (1994) obtained after intravenous administration was analysed by the present enterohepatic circulation model using NONLIN. The pharmacokinetic parameters were estimated, and the averaged concentration profile was obtained according to equation 14.

To examine the effect of sampling points and sampling time on parameter estimation, the hypothetical time-course data after oral administration was simulated and curve

fitting was performed using all the data or part of the data by omitting some sampling points.

Results and Discussion

Simulation of the time-course profile was performed by varying the values of the parameters of interest. Figure 2 shows the effect of k_{B1} as an example. The AUC ratio from equation 9 is always 2, but the transfer rates from compartment B to compartment 1 are different. The secondary peak appears more clearly when k_{B1} is larger. Some drugs undergoing enterohepatic circulation show a shoulder-like secondary peak that can be explained by the value of k_{B1}.

According to equation 14, a time-course profile can be averaged and a monotonically decreasing phase can be simulated, and an example is shown in Figure 3. By averaging the waving time-course profile, the apparent half-life can be estimated to allow evaluation of drug accumulation during repeated dosing.

Figure 4 shows the results of curve fitting to a plasma concentration data set after intravenous injection (Gabrielsson & Weiner 1994) according to the two-compartment enterohepatic circulation model. The parameter estimates are listed in Table 1.

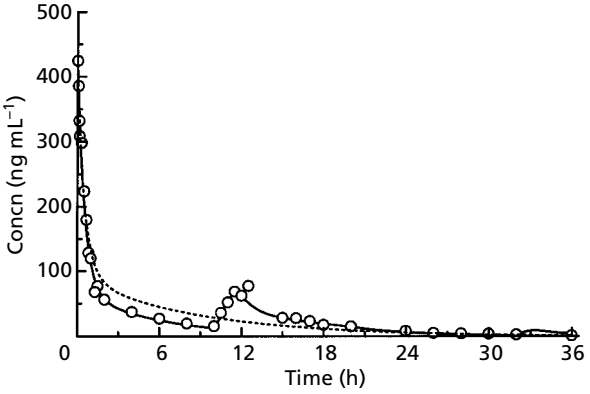

Figure 4 Result of curve fitting for the data of Gabrielsson & Weiner (1994). The solid curve is the fitting result and the dotted curve is the averaged plasma drug concentration profile.

Table 1 Parameter estimates by the curve fitting shown in Figure 4.

Parameter	Estimate	Standard error of estimate
ke (h^{-1})	0.434	0.238
V/F (L)	13.41	0.465
k_{1B} (h^{-1})	0.281	0.040
k_{B1} (h^{-1})	4.180	1.578
x (h)	21.79	0.377
u (h)	11.89	0.506
k_{12} (h^{-1})	0.878	0.112
k_{21} (h^{-1})	0.455	0.0868

Table 2 Generated hypothetical data set.

Time (h)	Concn (ng mL^{-1})	Time (h)	Concn (ng mL^{-1})
0.5	0.0	16	153.7
1	73.0	18	120.6
2	817.2	20	151.1
3	667.0	22	247.0
4	475.8	24	157.4
5	435.1	26	97.4
6	413.7	28	79.3
8	436.3	30	55.1
10	380.9	32	86.5
12	325.9	34	104.2
14	219.1	36	107.2

From these results and by using the equations given in the Appendix, the averaged half-lives were estimated to be 0.67 h and 6.1 h for the b- and c-phases, respectively. The standard errors of parameter estimates are small, indicating that they seem to be estimated correctly.

To examine the effect of sampling time on parameter estimation, a hypothetical data set was simulated based on the default parameter values described above and the random residual error (CV 15%, log-normal distribution) was added to each data point. The generated data are listed in Table 2.

Four data sets were considered based on the data in Table 2, the first being a full data set (n = 22), while in other sets, some points after 18 h were omitted (in the second set, data at 18, 22, 30 and 34 h were used (n = 16); in the third set, data at 22 and 24 h were used (n = 14); in the final set, data at 18 and 30 h were used (n = 14)). The parameter estimates are given in Table 3.

In all four cases, almost reasonable results were obtained, and the values in the case of the full data set gave parameter estimates almost the same as the original. In all data sets, enough data points at the secondary peak around 10 h were available, and these data made it possible to roughly estimate x and u values. In the second and third sets, we were able to use the 22-h data above the previously used data point (16 or 18 h), while in the case of the final data set, no peak data after 18 h were available. The deviation between the estimated x and u in the incomplete data sets seems to be dependent on the available data points, and the data at the third peak (around 22 h) seems to be important especially for correctly estimating x and u. The half-lives were estimated to be longer in the second and third data sets and underestimated in the fourth data set. This suggests that estimation of the half-life also depends on the data points. Standard error (s.e.) estimates are also shown in Table 3. These values should be carefully compared because the numbers of data points are different among the four data sets. With the full data set, some s.e. values especially for ka and T_{lag} were large because the number of data points at absorption phase was small and the prediction residual for 1-h data was much larger than those in other data sets. In other parameters, no clear dependence of s.e. on the number of data was found and it seems difficult to

Table 3 Parameter estimates by the curve fitting to simulated data.

Parameter	Original	Full data set	Data at 18, 22, 30 and 34 h	Data at 22 and 24 h	Data at 18 and 30 h
ka (h^{-1})	10.0	11.97 (197.85)	6.46 (17.45)	17.82 (12.88)	3.30 (2.37)
ke (h^{-1})	0.1	0.095 (0.065)	0.075 (0.150)	0.078 (0.028)	0.108 (0.016)
V/F (L)	100.0	98.9 (68.8)	100.5 (32.9)	102.3 (4.1)	105.4 (8.0)
k_{1B} (h^{-1})	0.1	0.094 (0.094)	0.136 (0.218)	0.130 (0.032)	0.099 (0.031)
k_{B1} (h^{-1})	0.5	0.468 (0.841)	0.421 (1.172)	0.422 (0.234)	0.875 (0.366)
x (h)	12.0	12.5 (3.2)	13.2 (4.2)	13.7 (0.6)	15.1 (2.5)
u (h)	6.0	7.39 (6.01)	8.03 (6.74)	8.96 (1.08)	9.76 (2.78)
T_{lag} (h)	1.0	0.737 (2.476)	0.835 (1.377)	0.996 (0.004)	0.970 (0.040)
$t_{\frac{1}{2}}$ (b)	13.4	14.2	21.6	20.4	9.5

Standard error is given in parentheses.

give a recommendation regarding the minimum number of data for accurate parameter estimation. Rather than that, it seems to be more important to obtain data at around peaks than to simply increase the number of data points.

For parameter estimation in this enterohepatic model, enough data points for concentration data are required and sampling schedule is to be well designed. Once the parameter estimates are obtained, an enterohepatic circulation model can be used for simulation in further stages for drug development. Especially a model considering enterohepatic circulation can predict a trough (minimum) concentration, while the concentration at just before the next dosing is not necessarily the minimum concentration.

In the presence of enterohepatic circulation, it is difficult to estimate the elimination half-life by the traditional models. In this model, by averaging the waving time-course profile, the apparent half-life can be estimated, which enables us to evaluate drug accumulation during repeated dosing.

In this model, x represents a cycle of enterohepatic circulation and the number of cycles within a dosing interval can be adjusted by changing the value of x. Although the present model assumes a periodic enterohepatic circulation, this model can be expanded to the case that enterohepatic circulation occurs at unequal time interval by adding another periodic parameter.

Conclusion

The present new pharmacokinetic model for analysis of enterohepatic circulation including the sine function seems to be useful for explaining plasma concentration profiles showing significant secondary peaks for profiles following single and repeated dosing. Moreover, by using the averaged transfer rate constant given by equation 14, the apparent elimination half-life, which has been difficult to estimate, can be computed and this parameter is useful for evaluating the accumulation during repeated dosing.

In this model, we tried to describe the effect of the enterohepatic circulation phenomenon on time-course profiles by introducing the sine function with only two additional parameters, x and u, into the classical (conventional) compartment model. These parameters, of course, do not correspond to physiological factors, such as the emptying time of the human gallbladder, and are used only for the purpose of mathematical explanation of the observed data. A merit of this model is that it can describe the concentration profile after repeated dosing without additional parameters for the single dosing model. The enterohepatic circulation models with gap time require extra gap time parameters for each dosing and moreover the gap time has been usually defined arbitrarily (i.e., sometimes it is not the pharmacokinetic parameter to be estimated). In our model, the periodic parameters x and u can be estimated by the curve-fitting technique. This is another merit of our new model. One disadvantage of our model is that it cannot apply when enterohepatic circulation occurs at unequal time intervals, and requires additional parameter(s) for unequal x, which is also required even for traditional enterohepatic circulation models.

We also wish to emphasize that the present model can estimate the averaged half-life from the results of curve fitting. The averaged half-life is an apparent value but it is important for estimating the drug accumulation during repeated dosing.

Appendix

Three solutions x_1, x_2, x_3 of the following cubic equation (A1) can be obtained as follows:

$$x^3+a\cdot x^2+b\cdot x+c = 0 \quad \text{(A1)}$$

$$P = (a^2-3b)/9, \quad Q = 1/54(2a^3-9ab+27c) \quad \text{(A2)}$$

$$h = \arccos(Q/\sqrt{P^3}) \quad \text{(A3)}$$

$$x_1 = -2\sqrt{P}\cos(h/3)-a/3 \quad \text{(A4)}$$

$$x_2 = -2\sqrt{P}\cos[(h+2p)/3]-a/3 \quad \text{(A5)}$$

$$x_3 = -2\sqrt{P}\cos[(h+4p)/3]-a/3 \quad \text{(A6)}$$

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