A Model with Separate Hepato-Portal Compartment ("First-Pass" Model): Fitting to Plasma Concentration-Time Profiles in Humans

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Purpose. To demonstrate the value of "first-pass" pharmacokinetic models (FPMs) in which the hepato-portal (HP) system is kinetically separated from the central compartment in fitting pharmacokinetic data obtained after intravenous (IV) and oral administration.
Methods. Plasma concentration-time profiles of an investigational drug obtained in six healthy subjects each received 4 mg as an intravenous (IV) bolus dose and 10 mg as an oral solution served as a real data example. The common three- and four-compartment models with the first-order absorption and lag time (3CM and 4CM, respectively) in which HP system is assumed to be part of the central compartment were used as alternative models. We tested also: (i) the sensitivity of the output of FPM to variations in its parameters assuming IV and oral administration; (ii) practical estimability of the FPM parameters by fitting it to 20 simulated noisy data sets; (iii) distinguishability of FPM, 3CM and 4CM by fitting them to the simulated data sets.
Results. FPM was shown to give the best fit as compared to 3CM or 4CM in 5 subjects of 6. The sensitivity of FPM was sufficient for the sake of parameter estimation. The "individual" means of parameter estimates obtained after fitting simulated data did not differ significantly from the preselected values. The variance in "individual" estimates was dependent on the sampling frequency. FPM was demonstrated to be distinguishable among relevant models.
Conclusions. FPM is preferable as compared to standard compartmental models for drugs extensively taken up by the intestine and/or the liver, and may have a broad spectrum of applications.

KEY WORDS: compartmental pharmacokinetic models; "first pass" effect; distribution; liver; intestine; sensitivity analysis; parameter estimability; NONMEM.

INTRODUCTION

The "first-pass" pharmacokinetic models (FPMs) in which the liver (or, more generally, the hepato-portal system) is represented by a compartment kinetically separated from the central one (an example is shown on Fig. 1) were suggested long ago (1) and have been extensively used since then to derive relationships characterizing presystemic elimination of drugs, particularly, integrated equations for oral bioavailability, clearance, etc. (2). Physiologically, the liver belongs to the highly perfused lean tissue group and usually can hardly be distinguished from the central compartment having only plasma concentrations after intravenous (IV) and oral administration. That is why FPMs have been applied to fit real plasma concentration-time profiles only rarely (3,4). Some drugs, nevertheless, are extensively taken up by intestinal and/or hepatic tissues, and their retention in the hepato-portal (HP) system after oral administration results in delayed absorption and significantly contributes to the overall mean absorption time (5). To model this delay using standard mammillary compartmental models in which the HP system is part of the central compartment one has to include an absorption lag time parameter (t_{lag}). However, FPMs with the separate HP compartment may give more adequate description of profiles and may have other advantages over standard models.

In this work, we applied FPM to the data obtained after IV and oral administration of an investigational drug to healthy subjects and found that it described plasma concentration-time profiles better than standard models. To be sure that FPM is practically identifiable under the actual input/output conditions we performed the sensitivity analysis and tested the estimability of parameters. Also, the distinguishability of FPM in a group of relevant models was assessed.

MATERIAL AND METHODS

Models and Their Fitting to Plasma Concentration-time Data

FPM used is shown on Fig. 1. It is parameterized in terms of apparent intrinsic HP clearance (CL_{int}) that corresponds to the total (free plus bound) plasma concentration, apparent compartment volumes and distributional flows. All parameter symbols are explained in the legend. The drug concentration in the central (sampled) compartment equals that in plasma. There is a separate HP compartment, and the only elimination pathway is assumed from the latter. IV dose directly enters the central compartment while after oral administration the drug passes HP compartment before reaching the central one. The model has also two peripheral compartments which account for the drug distribution into other body tissues.

FPM under consideration incorporates, in fact, the "well-stirred" liver model (6,7). Parameters of the former can easily

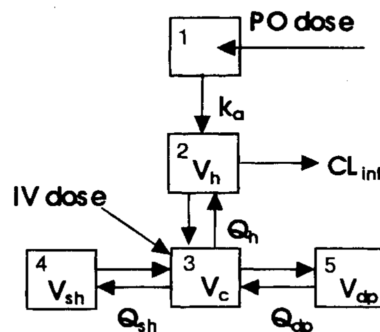

Fig. 1. The structure of FPM used in the study. Compartments are: 1, absorption depot compartment; 2, HP compartment; 3, central (plasma) compartment; 4 and 5, shallow and deep distribution compartments, respectively. Model parameters are: k_a, the absorption rate constant; V_h, the volume of HP compartment; V_c, the volume of central compartment; V_s and V_d, the volumes of shallow and deep peripheral compartments, respectively; Q_h, the effective HP plasma flow; Q_s and Q_d, the effective flows to shallow and deep compartments, respectively; CL_{int}, the apparent intrinsic HP clearance.

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be converted into non-compartmental parameters. Particularly, the hepatic extraction ratio,

$$E = \frac{CL_{\text{int}}}{Q_{\text{h}} + CL_{\text{int}}},$$

the total clearance, $CL = E \cdot Q_h$; the oral bioavailability, $F = 1 - E$. The steady-state volume of distribution, V_{ss}, can be calculated as the sum of the volumes of all FPM compartments.

Alternatively to FPM, the standard three- and four-compartment mammillary models that incorporated the central and two or three peripheral compartments (3CM and 4CM, respectively) were applied. Elimination was assumed to occur from the central compartments, and the absorption followed the first order with a lag time.

The NONMEM (version IV level 1.2) and NM-TRAN (version III level 1.1) programs (8) installed on HP-9000 workstation operating under HP/UX were used. The ADVAN7 library model of PREDPP subprogram (version II level 1.3) was selected. The latter gives a unique opportunity to fit linear models without solving (analytically or numerically) the corresponding systems of differential equations. When applying to individual pharmacokinetic data, NONMEM minimizes, in fact, the extended least squares objective function (8). The variance model selected was a sum of proportional and additive residual errors. To choose the best model, minimal objective function (MOF) values and Akaike Information Criterion (AIC) were taken into consideration.

Human Pharmacokinetic Data

The data used in this work were part of the Phase I study data file of an investigational drug (IND). Six healthy male volunteers (28–39 yr., 63–100 kg) were dosed intravenously (4 mg bolus dose) and orally (10 mg in solution). The time interval between two administrations was long enough to avoid carry-over effects. Venous blood was sampled frequently (starting from 2 min. after IV dose, and from 10 min. after oral dose) till 48 h post dose. Plasma was assayed for IND using a method based on high-performance liquid chromatography with the quantification limit of 1 ng/mL and the coefficient of variation of about 5%. The last sample with quantifiable IND level was usually of 32 and 48 h after IV and oral dose, respectively.

Non-compartmental pharmacokinetic parameters of IND were calculated from plasma concentration-time data using standard formulas (2). Particularly, CL was assessed as the ratio of IV dose to a corresponding area under the curve from zero to infinity (AUC). The oral clearance (CL_{po}) was approximated by the ratio of dose to AUC after oral dosing. Oral bioavailability was calculated as CL/CL_{po}. The central volume of distribution was calculated as the IV dose divided by the plasma concentration extrapolated to time zero. V_{ss} was assessed as CL*AUMC/AUC where AUMC is the area under time*concentration *versus* time curve after IV administration. AUC and AUMC were calculated using combined linear and logarithmic trapezoidal rule with the extrapolation to infinity according to standard formulas (2).

Sensitivity Analysis

Model parameters can be estimated only if an output (in our case, the plasma concentration, C(t)) is sensitive to variations in parameters. The sensitivity analysis of the FPM (Fig. 1) was performed by calculating the normalized (dimensionless) sensitivity coefficients, S(t), for each model parameter, P:

$$S(t) = \frac{dC}{dP} \cdot \frac{P}{C} \tag{1}$$

S(t) represents the percentage change in plasma concentration due to a percentage change in parameter P as a function of time. To calculate the sensitivity coefficients the NONMEM and NM-TRAN programs were applied with a specially designed NM-TRAN control stream file as follows. Each of nine model parameters was expressed as THETA(i) + ETA(i) (i = 1, 2, ... 9). In $ERROR block, 9 additional variables, DCDPi (i = 1, 2, ... 9), were defined and were equated initially to zero. The corresponding sensitivity coefficients were expressed in $ERROR block as DCDPi*THETA(i)/F where F is the model prediction (do not confuse with the oral bioavailability). Then the program was run, and the generated FSUBS file was inspected to identify variable names corresponding to the first derivatives of the model prediction with respect to ETA(i) calculated by the program. Then the control stream was revised by including into the $ERROR block the Verbatim code expressions equating DCDPi to these variables (see Appendix). Finally, NONMEM was run with the data file having a lot of time points to obtain sensitivity coefficients *versus* time curves. For the sake of comparison the same analysis was performed also for 3CM.

Parameter Estimability

We tested the practical estimability of parameters of the model depicted on Fig. 1 under actual input/output conditions. The approach similar to that described in (9) was applied. First, "individual" concentration-time profiles were generated using a $SIMULATION option of the NONMEM program. The values chosen for model parameters (core values) were close to the medians of individual estimates obtained after fitting FPM to IND data (see Table 1). The combined proportional-additive residual error model was used with the coefficient of variation 0.05 for the proportional component and the additive standard error of 1 ng/mL. These corresponded to the assay error and detection limit of the analytical method used in the IND study, and also were close to the estimates of residual errors got after fitting FPM to the IND plasma concentration-time data (see Results). Two curves were simulated for each "individual", one assuming IV bolus administration of 4 mg dose, and the second assuming 10 mg oral dose. In order to test the role of sampling protocol two schemes were used. One (sampling protocol I) was the same as used in the IND study (12 points per dose, 24 points per subject), while in protocol II there were 20 points per dose, 40 points per subject. Totally, twenty "individual" data sets were generated for each protocol. FPM was then fitted to these data sets and the resulting "individual" parameter estimates were treated in terms of mean prediction error (ME) and root mean squared prediction error (RMSE) according to (10). All errors were expressed in per cent relative to the core values of corresponding parameters. For the sake of comparison, the same approach was applied to assess the estimability of the 3CM parameters.

Model Distinguishability

Distinguishability means that the data generated assuming a particular model cannot be fitted equally well by applying

Table 1. Estimates of the "First-Pass" Model Parameters of an Investigational Drug in Healthy Male Volunteers

	Parameters									Residual error	
Subject #	CL_{int} L/h	V_h L	V_c L	V_s L	V_p L	Q_h L/h	Q_s L/h	Q_p L/h	k_a h^{-1}	Proportional, CV	Additive (ng/mL)
1	21.2	11.8	49.9	56.3	163	17.5	209	10.3	3.28	0.0612	1.13
	(14.6)	(15)	(8.1)	(8.0)	(52.2)	(13.8)	(32.1)	(12.5)	(8.5)	(31.0)	(27.3)
2	14.8	21.8	34.3	25.3	38.8	27	366	8.03	1.91	0.0711	1.5
	(3.68)	(10.7)	(9.5)	(16.8)	(19.7)	(11.2)	(13.8)	(30.9)	(7.5)	(41.6)	(27.7)
3	24.4	18	24.5	27.9	33.9	13.3	547	9.35	2.19	0.0466	1.54
	(5.9)	(8.3)	(35.5)	(21.6)	(20.4)	(8.8)	(39.8)	(60.2)	(7.8)	(58.1)	(36.4)
4	11.8	70.1	42.3	16.7	52.3	36.9	338	3.86	19	0.0809	1.03
	(7.50)	(18.7)	(7.8)	(24.8)	(56.8)	(12.7)	(41.4)	(42.7)	(68.9)	(17.4)	(31.2)
5	14.2	13.7	11.9	34.4	56.8	16	229	41.1	2.22	0.000008	2.17
	(4.54)	(10.4)	(2.7)	(7.5)	(7.8)	(9.3)	(2.1)	(16.4)	(6.1)	(85.6)	(12.3)
6	15.1	18.4	11.3	42.2	31.5	13.6	210	6.42	1.82	0.000002	1.79
	(4.34)	(21.6)	(2.1)	(5.7)	(15.9)	(7.6)	(1.8)	(45.5)	(18.4)	(137.4)	(13.5)
Min	11.8	11.8	11.3	16.7	31.5	13.3	209	3.86	1.82	0.000002	1.03
Median	14.95	18.2	29.4	31.15	45.55	16.75	283.5	8.69	2.205	0.0539	1.52
Max	24.4	70.1	49.9	56.3	163	36.9	547	41.1	19	0.0809	2.17

Note: Symbols are explained in the legend to Fig. 1. In parenthesis asympthotic standard deviations as estimated by the NONMEM program are given.

other relevant models. We fitted 3CM and 4CM to the simulated data sets that were used in testing the estimability parameters. Resulting MOF values were compared with those obtained after fitting the FPM, and the percentage of best fits obtained with the latter was calculated. Afterwards, new noisy data sets (20 "individual" profiles after IV and oral dosing) were simulated using 3CM according to the method described in the previous section. The core parameter values used in simulations were close to medians obtained after fitting 3CM to IND data (not shown). Again, two sampling protocols (I and II) were assumed. The "individual" data sets were then fitted using FPM and 3CM, and MOF values were compared.

RESULTS

Fitting Human Plasma Concentration-Time Data

An example of individual concentration-time data is shown on Fig. 2 (A). The data of other subjects looked similar. An example of the best fit curves are also shown on Fig. 2 (A). The weighted residuals (Fig. 2, B) randomly scattered around zero. In Table 1 parameter estimates are presented together with their standard errors. As the latter are rather small (with few exceptions) parameters are well-defined in almost every subject. There were also low covariance between parameters (not shown).

3CM and 4CM fitted to the same data gave worse results. Resulting MOF and AIC are compared in Table 2. The smallest AIC was obtained with FPM in all subject, but #1. By contrast to FPM, the variance-covariance matrix and standard errors of estimates were unobtainable for 3CM and 4CM in many subjects. FPM also predicted oral curves around the maximum better than 3CM (Fig. 3).

The coefficient of variation of the proportional component of the residual error (median, 0.053) as estimated with FPM was close to that of the assay method used (0.05), and the additive residual error (median, 1.5 ng/mL) was close to the limit of quantification (1 ng/mL).

Sensitivity Analysis

The sensitivity coefficient versus time plots are shown on Fig. 4. In the case of IV administration, the plasma concentration was most sensitive to variations in the central volume of distribution (within 1 h post dose) and in the intrinsic hepatic clearance (12 h after the dose and later) while the sensitivity to variations in V_h and Q_h was the lowest (the absolute value of

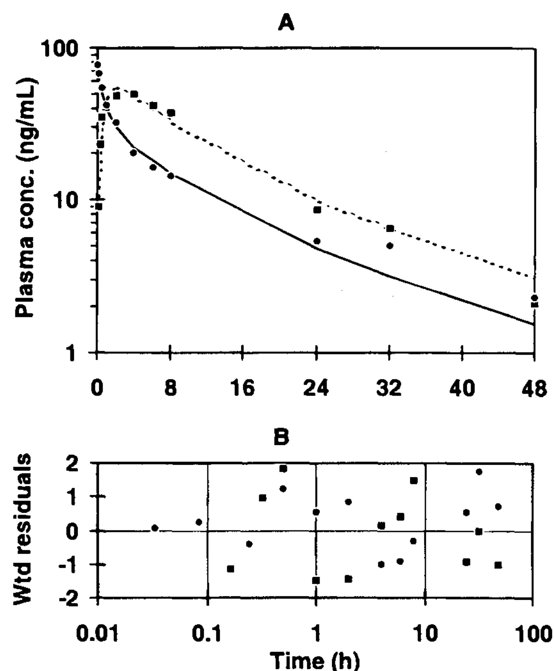

Fig. 2. A: Measured (symbols) and model-predicted (lines) plasma concentration-time profiles of an investigational drug in a healthy volunteer (#4) after intravenous (circles and a solid line) and oral (squares and a dotted line) administration. B: Weighted residuals *versus* time (logarithmic scale) plot.

Table 2. Minimum Values of the Objective Function (MOF) and Akaike Information Criterion (AIC) Corresponding to the "First-pass" Model (FPM) Shown on Fig. 1 and the Standard Three- and Four-Compartment Models (2CM and 4CM) with the Elimination from the Central Compartment

Subject #	FPM (9 parameters) MOF	AIC	3CM (9 parameters) MOF	AIC	4CM (11 parameters) MOF	AIC
1	50.583	68.583	42.891	60.891	42.89[a]	64.89
2	71.846	89.846	81.533[a]	99.533	82.789[a]	104.789
3	58.361	76.361	61.127	79.127	55.013	77.013
4	66.287	84.287	69.032[a]	87.032	71.094[a]	93.094
5	63.731	81.731	71.63[a]	89.632	154.37[a]	176.372
6	49.843	67.843	72.076	90.076	NC[a]	

[a] Ill-conditioning, no variance-covariance matrix available. NC: no convergence.

S less that 0.2). On the opposite, after oral dose the sensitivity with respect to V_h and Q_h was quite high (0.5 in modulus near 1 h post dose). This is not surprising taking into account that the delay in appearance of the drug in plasma is directly related to these two parameters. The highest sensitivity coefficients were those with respect to k_a (around 1 h after dosing) and CL_{int} (later than 10 h). Thus, one can conclude that the output of FPM was sufficiently sensitive to allow the estimation of parameters.

As it can also be seen, in general, the sampling schedule for the IND study was adequate since samples were taken in the ranges where the sensitivity of the model outputs to variations in parameters was the highest.

The same analysis of 3CM demonstrated the sensitivity coefficient for oral bioavailability was close to unity within the whole time range after oral dose. By the contrary, for t_{lag}, S(t) markedly differed from zero only when $t < 1$ h. The sensitivity to variations in other parameters was in the same range as in case of FPM.

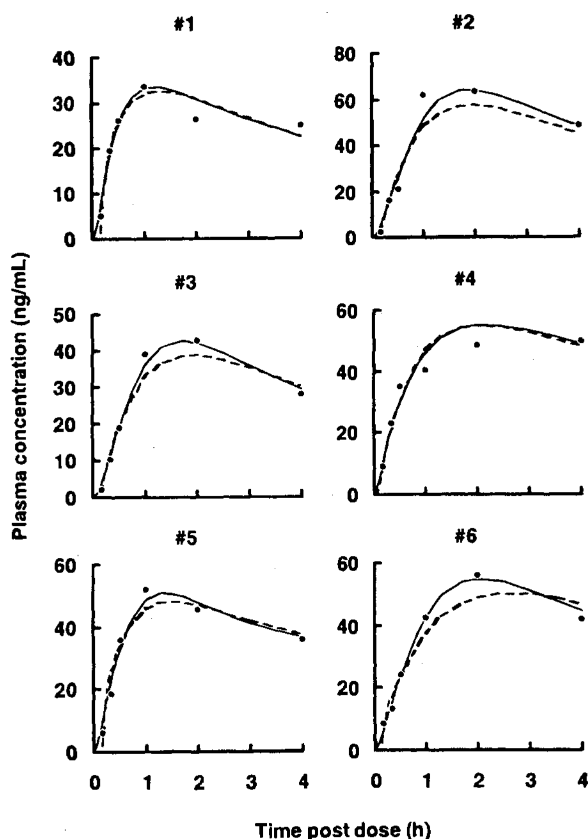

Fig. 3. Measured (circles) and model-predicted (lines) plasma concentrations of an investigational drug after oral administration of 10 mg to healthy volunteers (##1–6). The "first-pass" model and the standard three-compartment model predictions are shown in full and dashed lines, respectively.

Parameter Estimability

Table 3 compares mean prediction errors of parameters obtained after fitting FPM and 3CM to "individual" data sets generated with core parameter values shown also in Table 3. ME is known to be the measure of prediction bias, and in the case of FPM there were only 2 structural parameters with more than 5% bias: V_h and V_p. Both residual error parameters were also biased. Other structural model parameters were estimated accurately. With the sampling protocol II, there was almost no bias in all structural parameters; also the bias in residual error parameters was substantially reduced (not shown). The precision of parameter estimates expressed in terms of RMSE was excellent for CL_{int}, and could not be further improved by more frequent sampling. For Q_h it was also very good, but for other FPM parameters the precision was moderate. However it became substantially better with the sampling protocol II. The same was true for the residual error parameters. 3CM did not differ significantly from FPM with respect to estimability of parameters. The sampling protocol II also gave better accuracy and precision, however, the effect of more frequent sampling was less significant in this case as compared to the FPM (results not shown).

Model Distinguishability

When fitted to the data simulated on the basis of FPM, the latter gave the best fit in 65% of "individual" data sets with the sampling protocol I. More frequent sampling resulted in increased distinguishability of FPM: 75% of "individual" sets were better fitted by the latter, and only in 5 "individuals" of twenty 3CM or 4CM produced the best fit.

The "individual" data sets simulated on the basis of 3CM with the sampling protocol I were fitted preferably by the FPM as compared to the original model only in 2 cases of 20, and there were no cases where FPM was preferable over 3CM with the sampling protocol II.

Thus, the distinguishability of FPM among the group of relevant models can be assessed as substantial under the sampling protocol I and excellent with the sampling protocol II.

Pharmacokinetic Parameters of IND

Table 4 gives the summary of pharmacokinetic parameters of IND calculated on the basis of parameters of FPM presented in Table 1. The estimates obtained using non-compartmental formulas (2) are also shown. There were no significant differences in mean values of parameters assessed by modeling and by the non-compartmental approach. Moreover, a significant

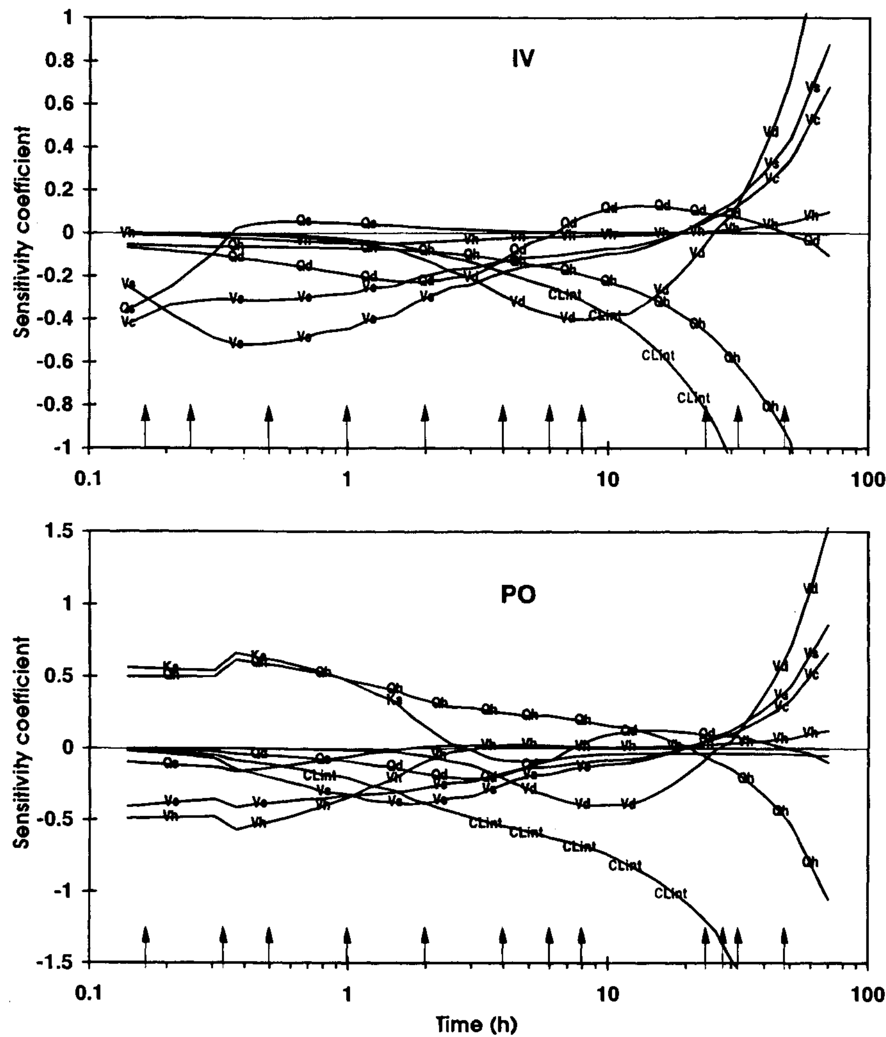

Fig. 4. Sensitivity coefficient *versus* time plots after IV and oral administrations for the FPM shown on Fig. 1. Parameter symbols (see the legend for Fig. 1) mark the corresponding curves. Arrows show the sampling times used in the study of the investigational drug.

Table 3. Results of Testing the "First-Pass" Model (FPM) and the Three-Compartment Model (3CM) Parameter Estimability

FPM parameters	CL_{int}	V_h	V_c	V_s	V_d	Q_h	Q_s	Q_d	k_a	Proportional error (CV)	Additive error
Core values	17 L/h	23 L	28 L	35 L	63 L	21 L/h	330 L/h	14 L/h	5.2 h^{-1}	0.05	1 ng/mL
ME (%)	−0.29	−8.84	3.68	−0.71	5.61	−0.60	−1.20	4.49	−0.74	−50.01	−9.84
RMSE (%)	4.8	27.8	18.3	12.3	18.8	9.1	31.5	28.3	36.6	60.3	30.7

3CM parameters	CL	V_c	V_s	V_d	Q_s	Q_d	k_a	T_{lag}	F	Proportional error (CV)	Additive error
Core values	8 L/h	36 L	60 L	70 L	205 L/h	51 L/h	1.1 h^{-1}	0.1 h	0.5	0.05	1 ng/mL
Me (%)	−0.04	−4.88	0.70	4.79	11.24	0.24	−3.05	−5.73	0.84	−46.00	−23.50
RMSE (%)	4.3	7.9	28.5	27.0	17.8	51.4	10.4	14.0	3.8	62.4	31.9

Note: ME is the mean relative difference between preselected (core) parameter values and "individual" estimates obtained by fitting the models to 20 sets of simulated data. RMSE equals to the square root of the mean squared relative differences. There were 24 time points in each of 20 data sets.

Table 4. Basic Pharmacokinetic Parameters of an Investigational Drug Calculated by Using a Non-Compartmental (Non-Comp.) Method and from the "First-Pass" Model (FPM) Parameters

	CL_{int} (L/h)		F		CL (L/h)		V_{ss} (L)		V_c (L)	
Subject	Non-Comp.	FPM	Non-Comp.	FPM	Non-Comp.	FPM	Non-Comp.	FPM	Non-Comp.	FPM
1	26.9	21.2	0.34	0.45	9.23	9.59	211	281	49.1	49.9
2	15.0	14.8	0.53	0.65	7.92	9.56	122	120.2	42.8	34.3
3	27.7	24.8	0.27	0.35	7.54	8.57	110	89.8	41.6	17.7
4	13.8	11.8	0.58	0.76	8.00	8.94	155	181.4	48.2	42.3
5	13.9	14.2	0.47	0.53	6.62	7.52	132	116.8	21.7	11.9
6	14.5	15.1	0.54	0.47	7.86	7.16	82	103.4	18.5	11.3
Mean	18.65	16.98	0.46	0.53	7.86	8.56	135.2	148.8	37.0	27.9
CV(%)	36.0	29.1	26.7	27.6	10.7	12.0	32.7	48.4	36.4	59.3

correlation between estimates of individual parameters normalized to their mean values was found ($Y = 0.01 + 0.95*X$, $r^2 = 0.79$, $P < 0.001$) indicating a close similarity between individual estimates of the same parameter obtained by two alternative methods. The intercept of the regression line and its slope did not differ significantly from zero and unity, respectively ($P > 0.1$).

DISCUSSION

Oral absorption of drugs is a complex process, and the plasma concentration-time profile after oral dosing depends on many factors. One of the most important factors that determine AUC is the "first-pass" metabolism which, in its turn, is the function of the activity of drug-metabolizing enzymes in the intestine and in the liver. However, the shape of the curve, particularly, the delay in the peak is dependent also on the drug distribution in the intestine and liver tissues. A pharmacokinetic model that is aimed to predict not only AUC, but also the shape of the curve must be complex enough to account for these distributional effects, at least for drugs significantly taken up by the intestine and/or by the liver. However, the model should not be too complex, otherwise the estimation of its parameters on the basis of typical pharmacokinetic data that usually include only plasma concentration-time measurements after IV and oral administration would be problematic.

FPM investigated in the present work (Fig. 1) seems to meet the above-mentioned requirements. It has been proposed first by Nagashima *et al.* (1), and has been used by Gibaldi *et al.* (11,12) to develop the well-known "first-pass" equations for the oral bioavailability. Since then, however, there were only few examples of using such type of models to describe time courses of drugs in blood or plasma (3,4).

We tried to fit FPM to plasma concentration-time data obtained after IV and oral administration of an investigational drug to healthy volunteers and found it preferable over 3CM and 4CM which included t_{lag} to model the absorption delay. FPM not only produced the best fit in terms of AIC, but, and this is very important, also converged better as compared to the standard models. The variance-covariance matrices and standard errors of parameters were obtained for all subjects in case of FPM as contrasted to 3CM and 4CM (Table 2).

To our knowledge, no sensitivity or identifiability analysis of FPM has been performed thus far. The sensitivity analysis is essential both for parameter estimability and for designing an optimal sampling schedule (13). We tested the sensitivity of the model outputs after IV and oral administration by calculating the normalized sensitivity coefficient as function of time elapsed after dose, and showed that it substantially differed from zero for every FPM parameter, at least, within a specific time range.

The practical estimability of FPM parameters was tested using noisy data sets generated assuming two sampling protocols differ in the number of blood samples taken. One of them (protocol I) was close to the actual conditions, while in the second one more frequent sampling (somewhat unrealistic for human pharmacokinetic studies) was assumed. Data shown in Table 3 clearly demonstrate that the FPM parameters are estimable fairly well with the sampling protocol I, and more frequent sampling, as expected, enhanced the estimability.

FPM from one hand, and 3CM and 4CM from other hand were demonstrated to be sufficiently distinguishable even with the sampling protocol I. That means, the models under consideration contrasted enough to be distinguished under real conditions.

So, the observation that FPM was preferable over 3CM in fitting the pharmacokinetic data of IND was not artificial. And it was not surprising since, according to results of animal studies, IND is extensively taken up by the small intestine and the liver. In the rat, liver-to-plasma and intestine-to-plasma concentration ratios were found to be greater than 30 within 0.25–2 h after oral dose (unpublished data). No data are available in humans, however, most probably, the drug is also distributed in a great extent in the HP system. IND was demonstrated also to be highly metabolized in man: only less than 1% of the dose is excreted with urine unchanged (unpublished data). It was shown to be completely absorbed from the gastro-intestinal tract after oral administration. The large volume of distribution in the HP compartment found in this work (26 L) which is comparable to that in central and shallow peripheral compartments was, therefore, in accord with the expected distributional pattern of IND.

The version of FPM used in the present work did not incorporate the plasma free fraction as a model parameter, however, it could easily be included. To estimate it, the free concentration should be measured together with the total plasma level, or, alternatively, individual estimates of free fraction

should be available to be fixed in the model. Unfortunately, none of them has been determined in the pharmacokinetic study of IND. From the other study it is known that IND is highly bound to plasma proteins, presumably to albumin (unpublished data). One could expect, therefore, that CL_{int} related to the free plasma concentration should be much higher than 15 L/h found in the present work on the basis of the total levels.

There is one more issue that complicates the interpretation of the FPM parameters, particularly, CL_{int}, but also Q_h. In its form used in the present work, FPM implies the "well-stirred" model of the liver which is only one (and the simplest one) of numerous possible models (14). By taking another model we could get different estimates for CL_{int}, as well as for Q_h. The selection of a proper liver model is, however, hardly feasible on the basis of existing data. However, the "well-stirred" liver model remains most suitable for including into a compartmental model like FPM.

That FPM is intimately related to the "well-stirred" liver model, immediately follows from the close similarity between estimates of its parameters found for IND and those calculated using non-compartmental formulas based upon the "well-stirred" liver model (see Table 4).

Despite obvious difficulties in interpreting FPM parameters (which are inherent not only for this particular model, but for any empirical compartmental model) it seems to be highly useful. At least, two important applications could be delineated. There is a great deal of studies on *in vivo/in vitro* correlations in which *in vitro* release kinetics is applied to predict various aspects of *in vivo* bioavailability, particularly, the time course of plasma concentration after administering controlled-release formulations (so-called level A correlation (15)). Since the oral plasma profile is dependent on the rate of drug input into systemic circulation rather than on the rate of release, no level A correlation is possible without taking into consideration the drug uptake by the HP system, at least for drugs highly accumulated in the intestine and/or the liver. FPM is thus a unique tool for such type of correlations allowing to simulate plasma concentration-time profiles after hypothetical administration of controlled-release formulations. *In vitro* release profile can be incorporated into FPM. The parameters of the latter, as it is shown in the present work, can be estimated from *in vivo* experiments with an immediate release formulation or drug solution.

The next area is modeling the drug-drug interaction *in vivo*. When analyzing results of such kind of studies, it is usually rather difficult to separate hemodynamic effects and the interaction at the enzyme level. There may be also displacement effects resulting in changes in volumes of distribution, particularly, in the liver. FPM provides a unique opportunity to quantify various interaction effects, and to simulate plasma level curves for variety of conditions (single dose, multiple doses, various dosing schemes for interacting drugs, etc.). Moreover, estimates of *in vivo* interaction parameters might be compared with *in vitro* estimates of the inhibition constant, K_I, or IC_{50} in order to derive clinically useful *in vitro/in vivo* correlations. Of course, to obtain the *in vivo* interaction parameters, a lot of studies should be performed, particularly, concentration-time profiles for both interacting drugs when administered simultaneously should be available.

In conclusion, FPM which incorporates the HP compartment kinetically distinguished from the central one was shown to be practically identifiable under conditions typical for clinical pharmacokinetic studies. It was successfully applied to fit the real plasma concentration-time data obtained after IV and oral administration of an investigational drug to six healthy volunteers. In 5 subjects of 6, the fit was better than that gained with the standard three- and four-compartment models incorporating an absorption lag time. The estimates of basic pharmacokinetic parameters were in agreement with those derived by non-compartmental methods. The problems associated with the interpretation of model parameters were discussed, and two possible applications of FPM were suggested.

APPENDIX

```
$PROBLEM FPM sensitivity analysis
$INPUT ID TIME EVID CMT DOSE=AMT RATE DV
$DATA sensdat.prn IGNORE=C
$SUBROUTINES ADVAN7 TRANS1
$MODEL
   COMP=(DEPOT)                                  ;1
   COMP=(HEPATIC)                                ;2
   COMP=(CENTRAL DEFOBS NOOFF)                   ;3
   COMP=(SHALLOW)                                ;4
   COMP=(DEEP)                                   ;5
$PK
   CLINT= THETA (1)+ETA (1)  ;INTRINSIC HEPATIC CLEARANCE
   VH=    THETA (2)+ETA (2)  ;HEPATIC
   VC=    THETA (3)+ETA (3)  ;CENTRAL
   VSH=   THETA (4)+ETA (4)  ;SHALLOW
   VDP=   THETA (5)+ETA (5)  ;DEEP
   QH=    THETA (6)+ETA (6)  ;HEPATIC BLOOD FLOW
   QSH=   THETA (7)+ETA (7)  ;DISTR. TO SHALLOW COMP
   QDP=   THETA (8)+ETA (8)  ;DISTR. TO DEEP COMP
   KA=    THETA (9)+ETA (9)

    K12=KA
    K20=CLINT/VH
    K23=QH/VH
    K32=QH/VC
    K34=QSH/VC
    K43=QSH/VSH
    K35=QDP/VC
    K53=QDP/VDP
    S3=VC
$ERROR
    DCDP1=0
    " DCDP1=D00190
    DCDP2=0
    " DCDP2=D00189
    DCDP3=0
    " DCDP3=D00188
    DCDP4=0
    " DCDP4=D00187
    DCDP5=0
    " DCDP5=D00186
    DCDP6=0
    " DCDP6=D00185
    DCDP7=0
    " DCDP7=D00184
    DCDP8=0
    " DCDP8=D00183
    DCDP9=0
    " DCDP9=D00182
;SENSITIVITY COEFFICIENTS
    SC1=DCDP1*CLINT/F
    SC2=DCDP2*VH/F
```

```
    SC3=DCDP3*VC/F
    SC4=DCDP4*VSH/F
    SC5=DCDP5*VDP/F
    SC6=DCDP6*QH/F
    SC7=DCDP7*QSH/F
    SC8=DCDP8*QDP/F
    SC9=DCDP9*KA/F

    Y=F+F*ERR (1)+ERR (2)
$THETA
    (0,12);            (1)
    (0,13);            (2)
    (0,30);            (3)
    (0,40);            (4)
    (0,60);            (5)
    (0,20);            (6)
    (0,280);           (7)
    (0,20);            (8)
    (0,3.5);           (9)
$OMEGA  .1 .1 .1 .1 .1 .1 .1 .1 .1
$SIGMA  0 FIX
        1 FIX
$SIMULATION (09834) ONLYSIMULATION
$TABLE TIME SC1 SC2 SC3 SC4 SC5 SC6 SC7 SC8 SC9
```

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REFERENCES

1. R. Nagashima, G. Levy, and R. A. O'Reilly. *J. Pharm. Sci.* **57**:1888–1895 (1968).
2. M. Gibaldi, and D. Perrier. *Pharmacokinetics*. 2nd edition. Marcel Dekker, New York, 1982.
3. G. Segre, A. I. Fiaschi, E. Bianchi, D. Ciani, and S. Tedeschi. *Arzneimittel-Forschung.* **38**:1846–1849 (1988).
4. D. Smith, W. Aldrich, M. Dey, R. Enever, R. Warner, and R. Weierstall. *Drug Metab. Dispos.* **18**:429–434 (1990).
5. W. L. Chiou. *J. Pharm. Sci.* **72**:1365–1368 (1983).
6. M. Rowland, L. Z. Benet, and G. G. Graham. *J. Pharmacokinet. Biopharm.* **1**:123–136 (1973).
7. K. S. Pang, and M. Rowland. *J. Pharmacokinet. Biopharm.* **5**:625–652 (1977).
8. S. L. Beal, and L. B. Sheiner. *NONMEM User's Guide. Part V.* University of San Francisco, San Francisco, CA, USA, 1992.
9. L. B. Sheiner. *J. Pharmacokinet. Biopharm.* **13**:515–540 (1985).
10. L. B. Sheiner, and S. L. Beal. *J. Pharmacokinet. Biopharm.* **9**:503–512 (1981).
11. M. Gibaldi, and S. Feldman. *J. Pharm. Sci.* **58**:1477–1480 (1969).
12. M. Gibaldi, R. N. Boyes, and S. Feldman. *J. Pharm. Sci.* **60**:1338–1340 (1971).
13. C. Cobelli, A. Ruggeri, J. J. DiStefano III, and E. M. Landaw. *IEEE Trans. Biomed. Eng.* **22**:249–256 (1985).
14. B. A. Saville, M. R. Cray, and Y. K. Tam. *Drug Metab. Revs.* **24**:49–88 (1992).
15. USP Subcommittee on Biopharmacokinetics. *Pharm. Forum.* 4160–4161 (1988).