Modeling of the Saturable Time-Constrained Amoxicillin Absorption in Humans

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Amoxicillin pharmacokinetics was modeled using a two-compartment disposition model and a saturable time-constrained absorption model with a storage compartment. The absorption model parameters estimated by the nonlinear regression are: a rate constant of the systemic input, k_{sys}, (median: 1.31 h^{-1}, range: 0.79–7.01 h^{-1}), a maximal absorption rate, V_{ma}, (median: 1407 mg/h, range: 703–4181 mg/h), an account corresponding to the half-maximal rate, K_{ma}, (median: 1077 mg, range: 235–4376 mg), time of the absorption cessation, T_{abs}, (median: 1.72 h, range: 0.82–4.53 h) and absorption lag time, T_{lag}, (median: 0.085 h, range: 0–0.123 h). It was shown, that the first-order absorption parallel to the saturable process is negligible in the dose range studied. The model described well the dependence of areas under concentration-time curves on the dose determined in several earlier studies. It was used also to predict the fraction of the amoxicillin dose absorbed for different doses. Simulations performed over a wide dose range (50–10000 mg) demonstrated that the fraction absorbed decreases nonlinearly from 90% at 50 mg to 22% at 10000 mg and strongly depends on the duration of the absorption period.

KEY WORDS: amoxicillin; absorption; human; dose-dependent; nonlinear; saturable; model; compartmental; time-constrained.

INTRODUCTION

Intestinal absorption of many drugs is or may be facilitated by some specialized transport mechanisms in animals (1–3) and in humans (4–9). Particularly, amino-β-lactam antibiotics, such as amoxicillin, cyclacillin, cephalexin, cephradine, cefadroxil, cefatrizine and others are absorbed by carrier systems (10,11) which are saturable and may be responsible for the reduction in the extent of absorption with increasing dose (5,12). Evidently, standard linear absorption models cannot be applied in these cases and alternative nonlinear models are to be developed. Recently, a model with saturable time-constrained absorption has been proposed (13). An extended version of this model has been successfully applied to ascorbic acid kinetics (14).

In this article, we applied a model with saturable time-constrained absorption to amoxicillin pharmacokinetic data obtained in 6 healthy volunteers who received 500 and 3000 mg amoxicillin orally and 500 mg intravenously (IV) (5). As the bioavailability of amoxicillin decreases with increasing dose, the construction of dosing schedules will benefit from the application of an adequate pharmacokinetic model.

METHOD

Amoxicillin pharmacokinetic data

Subjects, study design and basic results were described in details earlier (5) and are repeated here only briefly. Six healthy volunteers were given amoxicillin as 500 mg IV (5 min infusion) and 500 and 3000 mg orally. Blood samples were collected serially from 5 min to 10 h after dose. Amoxicillin concentrations in plasma were determined by high-performance liquid chromatography.

Models applied

Intravenous administration. According to the results of studies with IV administration of different amoxicillin doses (15) there are no signs of nonlinearity in its pharmacokinetics in a wide dose range (up to 5 g). Renal clearance has also been shown to be dose-independent up to 3 g dose (16). Thus, a standard two-compartment linear model with elimination from the central (sampling) compartment was selected according to (5,16).

Oral administration. Two models based on the linear two-compartment disposition model were considered (Fig. 1).

Model 1 is the same as used previously in the ascorbic acid bioavailability study (14). Compartments 1 and 2 are disposition compartments. Compartment 3 represents an absorption site (the intestine). Amoxicillin absorption can proceed by two parallel ways: a linear (first-order) process and a saturable pathway. The latter was supposed to be time-constrained: it operates only during some finite period of time, T_{abs}. For the time greater than T_{abs} the absorption rate by the saturable way becomes equal to zero.

Model 2 contains an additional compartment (number 4) between the absorption site and the central compartment. It may correspond to the gut wall that was shown to accumulate a certain amount of the drug in experiments *in situ* with rat intestine (10). The amoxicillin flux from the absorption site into compartment 4 proceeds by two parallel ways: a linear (first-order) process and a saturable one. As in the case of model 1, the latter was supposed to be time-constrained: it operates only when the current time is less than T_{abs}. The outcome indicated that the first order absorption rate constant k_{34} could be neglected because of its very low magnitude and high coefficient of variation. The differential equations for model 2 (without k_{34}) are shown in the Appendix.

Parameter estimation and model simulations

Model parameters from the set of differential equations shown in the appendix were estimated by nonlinear regression using ADAPT II package (17) slightly modified by us. The most important modifications consist in incorporating an absorption time lag and a subroutine for calculating the

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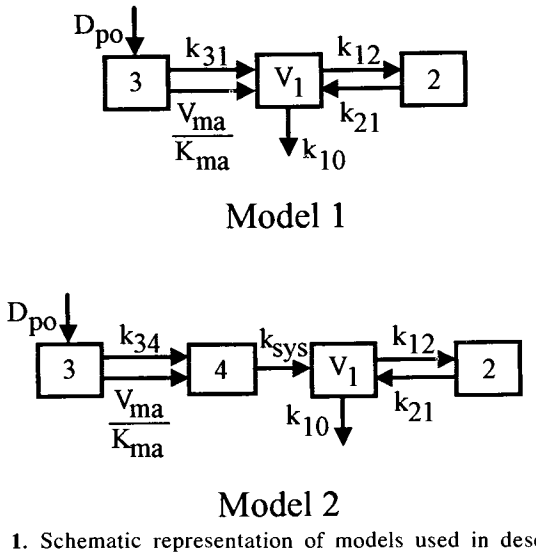

Fig. 1. Schematic representation of models used in describing amoxicillin kinetics. Symbols are explained in the text.

Akaike information criterion and Schwarz criterion (18) into the program. Three weighting schemes were tested: equal weights of the data, 1/C and $1/C^2$. Weights proportional to reciprocals of measured concentrations were selected because they balanced better the influence of measurement errors at very different amoxicillin concentrations.

Intravenous and oral data were treated separately. First, the two compartment model was fitted to the intravenous data and estimates of the central compartment volume (V_1) and the rate constants of exchange between compartments 1 and 2 (k_{12} and k_{21}) thus obtained were used in models for oral data as fixed (noniterated) parameters. Data on both oral doses were fitted simultaneously. The fit was repeated several times. First, T_{lag} and k_{34} together with V_{ma}, K_{ma}, k_{sys} and k_{10} were open for iterations, then T_{lag} and k_{34} were fixed equal to zero (one by one and both). The best model was chosen according to lower values of Akaike and Schwartz criteria and/or coefficients of variation of parameter estimates. The scatter of weighted residuals was also taken into consideration. To avoid local minima the program was always run several times with various initial values of parameters.

To simulate concentration—time and absorption rate—time curves the SIMTOOL program was applied. It is a macro program developed by us for the MS Excel spreadsheet package. It performs numerical integration of model differential equations shown in the Appendix and calculates model-predicted values of areas under concentration-time curves (AUCs) and amounts absorbed (A_{abs}) as a function of time (in tabular form). Particularly, amount absorbed was calculated as an integral of the systemic absorption rate equals $k_{sys} \cdot A_4$. It was demonstrated that A_{abs} did not increase after 9 h post dose. Thus a fraction absorbed (F) was assessed as a ratio of the amount absorbed up to 10 h to a dose administered.

Statistical analysis

Standard methods of descriptive statistics were used. Results were expressed as medians and ranges.

RESULTS

In Table 1 parameter estimates of the two compartment model for IV data are shown.

When trying to fit the data after oral administration, model 1 was shown to be absolutely improper. According to it the rate of absorption (the rate of appearance of the drug in the systemic circulation) is equal to the rate of amoxicillin disappearance from the absorption site, i.e. the absorption rate must be the highest initially and then should monotonically decline until the absorption stops. This contrasted with the results of deconvolution analysis of amoxicillin absorption presented earlier (5) according to which absorption rate-time curves were "bell-shaped".

Model 2 was shown to be adequate. It was found that in all subjects k_{34} in this model was negligibly low and had extremely high coefficient of variation. Both AIC and SC diminished when taking this rate constant equal to zero. So, the first-order absorption process parallel to the saturable one was insignificant in the dose range studied. Subsequently, this constant was not taken into consideration. In two subjects T_{lag} could also be neglected while in the other 4 subjects T_{lag} was significant.

Parameter estimates for the amoxicillin kinetic model after oral administration are presented in Table 2. Since there was a substantial interindividual variability in model parameter estimates and, most probably, they were non-normally distributed, medians were used throughout this work.

Fig. 2 demonstrates individual concentration-time

Table I. Parameters of the two-compartmental model of amoxicillin disposition in man after intravenous administration estimated by the nonlinear regression (CV is a coefficient of variation)

Parameter	Dimension	Subject						Median
		#1	#2	#3	#4	#5	#6	
V_1	L	10.70	9.53	8.74	14.26	10.71	13.79	10.71
CV	%	16	22	33	15	30	18	
k_{12}	h^{-1}	0.67	1.55	2.36	0.31	1.89	0.53	1.11
CV	%	85	74	96	108	96	107	
k_{21}	h^{-1}	1.12	1.51	2.50	0.70	2.02	1.06	1.31
CV	%	68	53	63	104	66	95	
k_{10}	h^{-1}	1.22	1.58	2.18	1.12	1.71	1.28	1.43
CV	%	18	24	32	16	30	20	

Table 2. Parameters of the saturable time-constrained absorption model in man after amoxicillin oral administration estimated by the nonlinear regression (CV is a coefficient of variation)

Parameter	Dimension	Subject						Median
		#1	#2	#3	#4	#5	#6	
k_{10}	h^{-1}	1.59	1.45	1.53	1.00	2.22	1.57	1.55
CV	%	12	32	27	63	10	13	
v_{ma}	mg/h	1715	849.4	2999	4181	1098	702.3	1407
CV	%	24	39	44	79	20	18	
K_{ma}	mg	234.5	1445	1250	4376	904	298.8	1077
CV	%	121	61	64	104	48	63	
k_{sys}	h^{-1}	0.79	1.24	1.38	0.90	7.01	3.73	1.31
CV	%	16	64	47	72	69	69	
T_{abs}	h	0.95	3.18	0.82	1.14	4.53	2.30	1.72
CV	%	19	19	24	24	11	12	
T_{lag}	h	0	0	0.116	0.114	0.055	0.123	0.085
CV	%	Fixed	Fixed	37	78	62	43	
V_{ma}/K_{ma}	h^{-1}	7.31	0.59	2.40	0.96	1.21	2.35	1.78
T_{abs}-T_{lag}	h	0.95	3.18	0.71	1.02	4.48	2.18	1.60

curves predicted with model 2 in comparison with measured data points. Low values of parameter coefficients of variations and the consistency between the model curves and the measured concentrations supported the acceptance of the model incorporating saturable time-constrained absorption and the storage compartment.

In Fig. 3 plasma AUC versus dose curve generated using model 2 incorporating median values of parameters estimated in this study (Tables 1 and 2) are compared with AUC estimates obtained by different authors. A relatively good agreement between predicted and measured values is evident.

Simulations were performed to evaluate the dependence of F on the oral dose and on the time of absorption cessation T_{abs} in the dose range 50–10000 mg (Fig. 4). In the case of T_{abs} = 1.72 h (the median of estimates obtained in this work) amoxicillin absorption is incomplete (F = 90%) even at the lowest dose (50 mg) and then decreases with increasing doses to 22% at 10000 mg. However, the slope of the curve shows the declining trend at higher doses. With shortening in T_{abs} the fraction absorbed diminishes while longer T_{abs} results in increasing F. In the case of T_{abs} = 3 h, low doses (up to approximately 300 mg) are almost completely absorbed.

DISCUSSION

A usual way to model the pharmacokinetics of drugs after oral administration consists in applying zero- or first-order kinetics for the absorption process, however, the mechanisms involved are complex and can hardly be expressed in terms of simple models. Two basic issues may be considered.

First, some amount of a drug absorbed from the gut lumen may reside in the intestinal wall and/or in the liver. Particularly, it has been shown (19) that the mean transit time of some drugs through the liver may vary from several minutes to 1 h. As the result of the retention in the intestinal wall

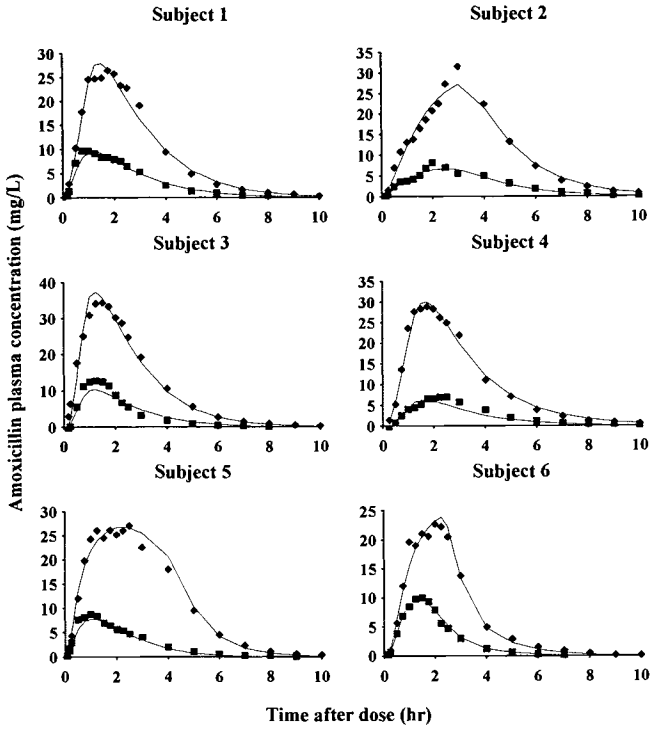

Fig. 2. Individual amoxicillin plasma concentration-time profiles after 500 mg (squares) and 3000 mg (diamonds) single oral doses. Lines represent model predictions obtained with the model 2 assuming no first-order absorption.

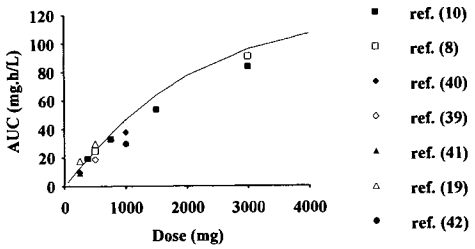

Fig. 3. The area under amoxicillin plasma concentration-time curve as a function of the oral dose. The line represents the model prediction; points are the AUC estimates taken from several sourses. The reference numbers are given alongside the point symbols.

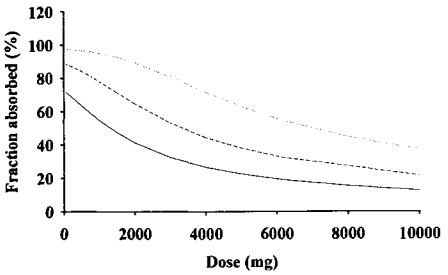

Fig. 4. Model-predicted dependence of the fraction absorbed on the amoxicillin oral dose for different values of absorption cessation time T_{abs}. The full line: T_{abs} = 1 h; the dashed line: T_{abs} = 1.72 h; the dotted line: T_{abs} = 3 h.

and in the liver the rate of drug appearance in the blood, in contrast with the simplest absorption models, is not equal to the rate of its disappearance from the absorption site. A numerical deconvolution analysis usually reveals this fact giving bell-shaped absorption rate-time profiles, as in the case of amoxicillin (5,20).

A delay between the absorption and the appearance of a drug in the systemic circulation could be introduced into a pharmacokinetic model by assuming some empirical function for the absorption rate which would reflect its bell-shaped pattern, as the Weibull function (21). Alternatively, a storage compartment can be inserted between the absorption site and the sampling compartment (22) as done in this work.

The second reason is a phenomenon known as a discontinuous or time-constrained absorption (23). The absorption is normally time-constrained simply because of the limited length of the intestine. The duration of absorption may be even shorter than the mean transit time through the intestine if a substantial part of the dose is absorbed by some specialized process, as it was shown for amoxicillin in rats (10,11), and if enzymes responsible for the absorption are distributed along a relatively short segment of the intestine.

However, these two mechanisms cannot explain the decrease in the fraction absorbed with increasing oral dose (24). A time-constrained linear (first- or zero-order) absorption may not explain a dose dependency of the fraction absorbed (6,13): the absorption rate must be dose-dependent (saturable). There may be different causes of nonlinearity in absorption rate, particularly, a limited solubility of a drug, as it has been hypothesized for chlorothiazide (25). In the case of amoxicillin, the problem of solubility has previously been discussed and shown to be insufficient to explain the nonlinearity of amoxicillin absorption (5). Thus, only a time-constrained absorption in association with a saturable kinetics could explain the dependence of the fraction absorbed on amoxicillin dose.

This principle has been successfully utilised recently in modeling of the ascorbic acid absorption kinetics (14). In the present work with amoxicillin, we have tried to apply the same model to amoxicillin data (model 1, Fig. 1), but failed and suggested a model with a storage compartment (model 2). It is an empirical model and its compartments are not more than mathematical abstractions. Nevertheless, compartment 3 may be regarded as representing the intestinal lumen, while compartment 4 represents the intestinal wall. The model has a saturable absorption pathway which is expressed in the form of a standard hyperbolic function. The meaning of parameters are as follows. V_{ma} is the maximal absorption rate (in mg/h) that reflects the overall capacity of the absorption process. Certainly, it is determined by the transport system capacity, but evidently may not be considered as an intrinsic measure of the latter. The same is true for K_{ma} equal to a drug amount in compartment 3 corresponding to the half of maximal disappearance rate. The ratio of these parameters (V_{ma}/K_{ma}, median: 1.78 h^{-1}, range: 0.59–7.31, see Table 2) can be compared with the value found in rat experiments *in situ* (2.26 h^{-1}, ref. 10). Taking into account the differences between our study and that by Nakashima et al. (10) the closeness is astonishing.

The saturable component of the absorption process in the model is assumed to be time-constrained: it operates only during a time interval T_{abs} minus T_{lag}. It was estimated to be 1.6 h (median; range: 0.95–4.48 h). This parameter may be regarded as an average or effective time during which the drug is in contact with a specialized transport system in the intestine. Of course, it is not possible to identify the exact intestine segment containing this system. Moreover, there may be two or more "active" segments differing in their absorption capacity, and this may account for some systematic deviations of data points from the model curves (Fig. 2).

Model 2 includes initially also a first-order passive absorption process parallel to the saturable one, but it was found to be negligible in accordance with the low lipid solubility of amoxicillin and experimental findings (10): the first-order absorption rate constant was shown to be more than 10 times lower as compared to V_{ma}/K_{ma}.

A storage compartment between the absorption site and the central compartment could be associated with the drug bound within the intestinal wall, as it was experimentally shown by Nakashima et al. (10). The rate constant k_{sys} regulates the appearance of amoxicillin in the systemic circulation (median: 3.73 h^{-1}, range: 0.79–7.01 h^{-1}). It is higher than V_{ma}/K_{ma} ratio (1.78 h^{-1}) showing that the retention of the drug in this compartment is not too prominent.

Two disposition compartments were included into model 2 and the exchange rate constants were assumed to be equal to those after intravenous administration. It is a usual practice in bioavailability studies, otherwise any model for oral administration may not be structurally identified (26). Of course, some intraindividual variations cannot be excluded, but they are probably small, as it can be seen in the case of k_{10} (cf. Tables 1 and 2).

The model of amoxicillin pharmacokinetics after oral administration developed enables not only to simulate plasma concentration-time curves (Fig. 2), but also to analyse the dependence of AUC and F on the dose administered.

A fairly close relation (Fig. 3) between AUCs evaluated by different research groups and those predicted by model 2 on a basis of median parameters estimated from the data of 6 subjects (5) can be seen. The model slightly overestimated AUC values for doses higher than 1000 mg, probably, because of some decline of our parameter estimates from true population means. Of course, more subjects are to be included in amoxicillin pharmacokinetic modeling.

Our model is applicable also for predicting amoxicillin bioavailability, particularly, the fraction absorbed as a func-

tion of dose and model parameters, for example, the duration of absorption (Fig. 4).

In conclusion, the application of a nonlinear time-constrained absorption model with a storage compartment enabled not only to estimate parameters of amoxicillin absorption in man which were in accordance with experimental findings, but also helps in predicting a dose-dependency of AUC and the fraction absorbed. The model could also be used to simulate amoxicillin plasma concentration-time profiles after multiple administration, however, a detailed simulation study was out of the scope of this work.

APPENDIX

Differential equations describing the model 2 (Fig. 1) without the first-order absorption rate constant are given below:

$$\frac{dA_1}{dt} = k_{sys}A_4 - (k_{12} + k_{10})A_1 + k_{12}A_2$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2$$

$$\frac{dA_3}{dt} = -R_a$$

$$\frac{dA_4}{dt} = R_a - k_{sys}A_4$$

where

$$R_a = \begin{cases} \dfrac{V_{ma}}{K_{ma} + A_3} \cdot A_3 & \text{if } t \le T_{abs} \\ 0 & \text{if } t > T_{abs} \end{cases}$$

Initial conditions:

$$A_1(0) = A_2(0) = A_4(0) = 0;\ A_3(T_{lag}) = D$$

where T_{lag} is the absorption lag time. For $0 < t < T_{lag}$ $A_3(t) = 0$. The plasma concentration is calculated as:

$$C = A_1/V_1$$

where V_1 is a central volume of distribution. The meaning of other model parameters is explained in the Discussion and is clear from the scheme given in Fig. 1.

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