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A Double-Peak Phenomenon in the Pharmacokinetics of Veralipride After Oral Administration: A Double-Site Model for Drug Absorption

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Equal doses of veralipride have been given to 12 healthy volunteers by three different administrations—intravenous infusion, oral solution, and oral capsules—in a randomized cross-over design. After the intake of the solution, but not after infusion or capsules, two maximum plasma concentrations have been observed and interpreted, according to a double-site model for drug absorption.

KEY WORDS: veralipride; pharmacokinetics; enterohepatic recycling; double site of drug absorption.

INTRODUCTION

Drug absorption from the gastrointestinal tract is generally considered to occur by passive diffusion throughout the gastrointestinal membrane. Nevertheless, some exceptions such as amino acids have been described (1) where active processes are involved. In the latter cases, first-order absorption, which is commonly used to characterize drug absorption, is unable to depict correctly the appearance of the drug in the blood stream. The same occurs for drugs that exhibit an enterohepatic recycling for which, even with a passive cross-membrane phenomenon, particular pharmacokinetic models have been developed (2,3,4,5,6). For such drugs, the

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reabsorption leads to nonmonotonicity in the shape of plasma concentration curves with the appearance of successive peaks (7). Other physiological phenomenon may explain such curves. In particular, unhomogeneous absorption of drugs through the gastrointestinal membrane could theoretically lead to a similar multipeak phenomenon. This was recently demonstrated for piretanide (8). We recently have studied a new drug, veralipride, in a dose-dependent pharmacokinetic design. In this study, a double peak in plasma concentrations was observed after oral administration of a solution, whatever the dose (9). In order to confirm and explore the physiological mechanisms involved in this result, the present work describes a study including the administrations of three unique doses of veralipride (intravenously and orally as a solution or a capsule) to 12 subjects. Although different models based on physiological processes could theoretically depict the observed data, we have been interested in developing the concept of an absorption window. Such a model has been previously presented for a single site of drug absorption (10). We have developed this concept to a double site of drug absorption. The application of this model to our data allowed us to depict correctly the double-peak phenomenon.

EXPERIMENTAL

Design of the Study

Twelve healthy volunteers gave informed consent to participate in the study. They were free from cardiac, pulmonary, hepatic, or renal diseases and allergies, according to a clinical and biological examination. None of them received any drug for at least a week, and for known inducers or inhibitors of hepatic enzymatic activity at least 1 month, before the study. Each subject received the three different pharmaceutical forms—intravenous infusion, oral solution and capsule—at 1 week intervals in a randomized cross-over design. In each case, a 100-mg dose was administered in the morning after an overnight fast. Oral administrations were performed using 200 ml of water and for the intravenous infusion, a 30-min constant rate of input was obtained by using an electric infusion pump (Braun). Subjects fasted up to 4 hr after drug administration in each case.

A 10-ml heparinized blood sample was withdrawn from the antecubital vein at times given in Table I. Blood samples were immediately centrifuged and plasma stored at −20°C until they were analyzed. Uring samples were also collected every hour during the first 6 h, every 2 hr during the next 6 hr, once during the next 12 hr, and every 24 hr during the next 5 days. A 30-ml aliquot of urine was stored at −20°C until analysis, after the measurement of volume and *p*H of each fraction. Biological samples were analyzed

Table I. Individual Plasma Concentrations of Veralipride (ng/ml) Observed After the Administration of 100 mg of Veralipride as a Solution

Time (h)	Subjects											
	A	B	C	D	E	F	G	H	I	J	K	L
0	0	0	0	0	0	0	0	0	0	0	0	0
0.17	571.7	229.4	52.8	233.2	220.5	259.9	13.4	18.1	83.1	211.1	143.3	95.5
0.33	780.0	243.6	96.8	241.4	300.3	358.2	64.9	28.1	214.9	508.3	321.6	386.3
0.50	629.3	206.9	138.3	218.8	560.0	231.9	219.0	40.3	336.8	844.9	365.6	323.8
0.75	551.7	153.4	148.6	198.9	501.7	184.4	304.0	106.0	259.9	668.7	433.8	226.2
1	432.0	140.0	164.6	169.8	310.6	155.7	301.3	168.3	222.4	542.4	406.9	197.0
1.5	361.9	152.0	143.6	196.7	333.7	148.6	267.9	264.7	206.1	456.6	372.5	177.0
2	352.6	184.9	131.7	232.4	318.8	223.5	221.3	247.8	234.4	301.6	342.5	180.6
2.5	303.6	248.3	144.4	249.6	337.4	227.8	253.9	307.9	276.9	336.5	273.3	187.4
3	329.7	264.9	154.9	227.8	287.4	245.7	343.1	343.9	280.9	251.6	221.5	209.5
4	244.5	209.9	166.2	201.3	434.1	220.7	240.6	270.8	280.1	216.2	200.8	339.0
6	120.7	162.2	117.6	147.7	311.8	136.9	132.5	152.8	212.1	145.3	128.1	199.4
8	63.0	137.5	109.1	114.8	270.4	93.9	90.9	105.0	188.6	102.8	81.2	148.2
10	31.7	127.4	90.5	65.1	109.5	70.1	62.2	76.6	122.6	86.0	59.5	102.7
12	11.6	97.0	80.5	33.4	111.4	47.2	39.6	49.6	88.8	46.4	41.9	91.1
24	0.0	45.7	43.2	1.3	31.1	16.3	17.8	31.3	38.7	32.0	18.7	17.5

using a gas chromatographic-mass spectrometric method previously described (9,12). Sensitivity was 10 ng/ml in plasma and 1 μg/ml in urine. The reproducibility was better than 10% in the tested ranges and a good linearity was obtained from 10 to 1500 ng/ml in plasma and from 1 to 100 μg/ml in urine.

Calculations

Plasma concentrations have been interpreted according to an open two-compartment model after intravenous infusion and a one-compartment open model after capsule administration, using an iterative procedure based on a Gauss-Newton algorithm (13).

To fit the oral solution data, we have used the following double-site absorption model shown in Fig. 1. This model is based on that described by Kubler (10) and Suverkrup (11) in which the orally administered drug goes through the intestinal lumen and reaches a specific intestinal segment where absorption occurs. Applied to a double segment where drug absorption occurs with first order and finite limits for each of them, combined with a uniform rate of transit through the intestinal lumen, the different phases of drug absorption can be characterized as follows:

Phase of Filling in Site I ($0 \leq t \leq T_1$). The amount of the drug being absorbed depends on both the amount of available drug, which increases

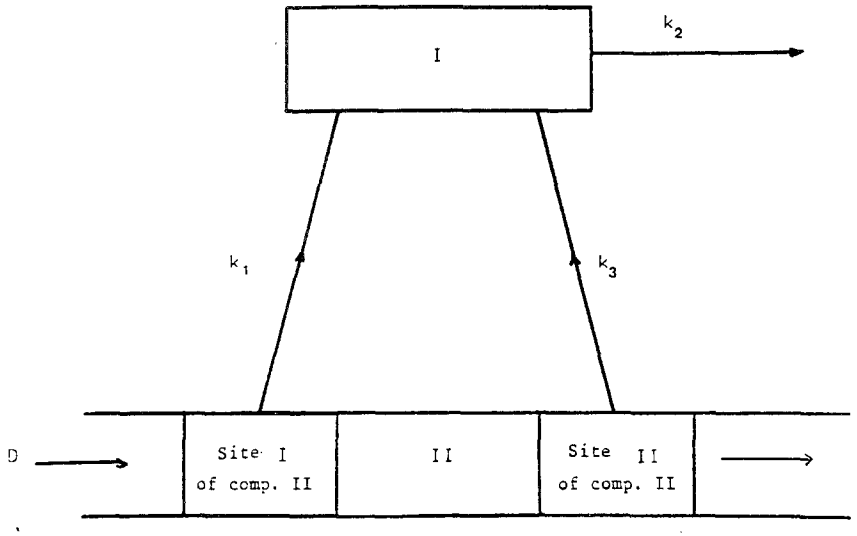

Fig. 1. Pharmacokinetic model involving two different sites of drug absorption. Compartment I stands for the body and compartment II for the gastrointestinal tract. k_1 and k_3 are the rate constant of absorption from the sites I and II, respectively, while k_2 is the rate constant of elimination.

uniformly until the entire administered dose lies within the segment at time T_1, and the absorption rate constant k_1.

Phase of Penetration in Site I ($T_1 \leq t \leq T_2$). Between times T_1 and T_2, the absorption can occur from the entire intestinal segment, all the available administered dose filling it.

Phase of Emptying in Site I ($T_2 \leq t \leq T_2 + T_1$). During this phase, the drug gradually leaves the absorbing segment, with the same rate constant so that no more drug remains in site I at time $T_1 + T_2$. Therefore, the fraction available for absorption decreases continuously.

At time $T_1 + T_2$. The amount of drug present in site I is equal to zero but a certain amount $A_{a,1}$ escaped from the first segment and is still present in the intestine.

Between $T_1 + T_2$ *and* T_3. Nonabsorbed drug moves through the intestine without further absorption. During this phase, the amount in the body continuously decreases due to the drug elimination.

Phase of Filling in Site II ($T_3 \leq t \leq T_4$). As previously for site I, the drug gradually reaches the second absorption segment from which it is absorbed with a rate constant k_3.

Phase of Penetration in Site II ($T_4 \leq t \leq T_5$). The remaining drug lies within the entire second segment from which it is absorbed.

Phase of Emptying in Site II ($T_5 \leq t \leq T_5 + T_4 - T_3$). During this phase, if the entire administered dose has not been absorbed earlier, the drug leaves the second intestinal segment so that, at time ($T_5 + T_4 - T_3$), nothing remains available for absorption.

After Time $t \geq T_5 + T_4 - T_3$. The drug that might remain in the intestine is not absorbed, so that nothing else can happen but elimination from the body.

During these phases, the absorbed drug is distributed and eliminated, as previously for capsule administration, according to a one-compartment open model, with a first-order elimination rate constant k_2. The Appendix describes the equations and the mathematical expressions of the amount of drug in the body as a function of the time. The corresponding computations have been performed on a Multics computer DPS 8 (Honeywell-Bull) using the nonlinear regression method of Marquardt (14).

Table II. Pharmacokinetic Parameters of Veralipride Calculated After the Different Administrations (Mean ± SD for 12 Subjects)[a]

Parameters	Units	Intravenous infusion	Oral solution	Oral capsules
$C_{max,1}$	ng/ml	1638.7 ± 232.6	401.5 ± 226.5	
$t_{max,1}$	hr		0.59 ± 0.36	
$C_{max,2}$	ng/ml		285.2 ± 82.6	362.3 ± 164.9
$t_{max,2}$	hr		3.04 ± 0.5	2.5 ± 1
t_{lag}	hr			0.69 ± 0.62
k_a	hr^{-1}			2.23 ± 2.39
$t_{1/2,k_a}$	hr			0.60 ± 0.49
λ_1	hr^{-1}	8.72 ± 3.33		
$t_{1/2,\lambda_1}$	hr	0.091 ± 0.03		
λ_2	hr^{-1}	0.28 ± 0.05	0.18 ± 0.08	0.22 ± 0.10
$T_{1/2,\lambda_2}$	hr	2.46 ± 0.41	4.42 ± 2.67	3.97 ± 2.25
AUC	$mg \cdot l^{-1} \cdot hr$	2.75 ± 0.44	2.60 ± 0.61	2.26 ± 0.50
CL	$l \cdot h^{-1}$	37.15 ± 5.9		
V_1	l	23.75 ± 10.82		
V_2	l	84.01 ± 12.98		
V_{SS}	l	150.5 ± 20.46		
CL_R	$l \cdot h^{-1}$	12.58 ± 3.6	13.54 ± 4.8	15.39 ± 3.01
$A_{e(\infty)}$	mg	46.77 ± 13.05	40.52 ± 10.7	43.88 ± 7.41
F	%		86.50 ± 31.05	78.63 ± 20.23

[a] The experimental data have been interpreted according to a two-compartment model following an intravenous infusion and a one-compartment model after ingestion of capsules. For oral solution, model-independent parameters were calculated. The first maximum occurs at time $t_{max,1}$, the second one at time $t_{max,2}$. The half-life periods $t_{1/2}$ have been calculated for absorption (k_a) and disposition (λ_1 and λ_2). V_1, V_2, and V_{SS} are model and steady-state volumes of distribution, respectively, while CL and CL_R denote the total plasma clearance and the renal clearance. $A_e(\infty)$ represents the total amount of unchanged drug excreted in the urine.

In all cases, the slope of the regression line of the unchanged veralipride urinary elimination and the plasma concentration at the corresponding midpoint time of urine collection was used to estimate the renal clearance reported in Table II. In addition, following intravenous administration, renal clearance was estimated by simultaneously fitting the plasma concentration and excretion rate data using the respective previously applied models. For each subject, a single set of exponential terms was able to describe adequately both the plasma concentrations and the urinary elimination of the drug ($r>0.95$ between observed and calculated values). The mean renal clearance values estimated with this method are indicated in Table II.

The statistical comparison of the pharmacokinetic parameters obtained after each administration was performed using a variance analysis including subject, route, and order of drug administration, according to the protocol.

RESULTS

Plasma Sample Analysis

Intravenous infusion

Each set of veralipride plasma concentrations obtained in the 12 subjects (available from the authors upon request) was systematically interpreted according to three different models, i.e., one-, two-, or three-compartment open models with a zero-order rate of input. At each step, the benefit of increasing the number of compartments was evaluated with a statistical Fischer test using the least squares criterion. This criterion showed us that the two-compartment open model was the most suitable in each case. The mean pharmacokinetic parameters (mean ± standard deviation) are listed in Table II. Seen is an initial rapid phase with a 0.091 ± 0.03 hr half-life (range: 0.05–0.14 hr) followed by a terminal phase with a 2.46 ± 0.41 hr mean half-life (range: 1.81–2.93 hr). The volumes of distribution are moderate, mean: 23.75 ± 10.83 L (range: 12.42–53.14 L) for the central compartment and 84.01 ± 12.98 L (range: 69.22–105.51 L) for the peripheral one. The total clearance estimated from the extrapolated area under the plasma curves is large, 620 ± 98 mL · min^{-1} (range: 455–802 mL · min^{-1}).

Oral Capsule Administration

The veralipride plasma concentrations obtained from the 12 subjects (available upon request) were interpreted as previously, a first-order absorption and a lag time being added in the different models. According to the Fischer test, these sets of data were better fitted using the one-compartment

open model, as generally occurs when interpreting intravenously or orally administrations.

The corresponding mean pharmacokinetic parameters are listed in Table II. Half-life periods and renal clearances are in the same range as those obtained after intravenous infusion.

In contrast, the area under the plasma curves differ significantly at the 0.05 level, the mean absolute availability being 78.6%.

Oral Solution Administration

The individual plasma veralipride concentrations obtained in the 12 subjects are given in Table I. These concentrations show for each subject two successive maximum concentrations, the first one occurring 0.59 ± 0.36 hr after drug intake and the second one occurring 3.02 ± 0.50 hr after it. That is, at a time corresponding to the maximum concentration observed after the capsule administration.

For these data, classical pharmacokinetic interpretation was impossible so that only the terminal phase half-life determined from a semilogarithmic plot using the least squares criterion and the area under the plasma curve using the trapezoidal rule were estimated. These parameters are listed in Table II. They are similar to those obtained with the two other routes of drug administration and the analysis of variance again failed to show any difference for these parameters except for the area under the plasma curves, so that the mean absolute availability of this form may be estimated at $86.5 \pm 30.05\%$.

For 9 of the 12 subjects, the double-site absorption model enabled us to obtain a satisfactory fitting of the data. An example of curves obtained after the solution administration in two subjects (G and H) is shown in

Table III. Pharmacokinetic Parameters Obtained by Optimization for Nine Subjects Using the Two-Site Absorption Model After the Administration of a Solution

	Parameters[a]								
Subjects	k_1 (hr^{-1})	k_2 (hr^{-1})	k_3 (hr^{-1})	T_1 (hr)	T_2 (hr)	T_3 (hr)	T_4 (hr)	T_5 (hr)	Volume (l)
B	0.995	0.230	6.655	0.99	1	2.26	2.53	2.58	201
C	0.995	0.231	6.576	1	1.01	2.26	2.53	2.58	202
D	1.019	0.234	5.976	0.96		2.28	2.54	2.55	202
E	1.615	0.173	5.012	0.25	0.92	2.25	2.6	5.01	175
F	1.007	0.235	5.946	0.96	0.98	2.28	2.54	2.54	203
G	1.638	0.272	5.783	0.42	0.59	2.31	2.60	2.60	176
H	1.04	0.232	7.0	1.01	1.02	2.24	2.53	2.56	200
J	1.495	0.218	5.341	0.25	0.95	2.28	2.5	2.53	186
K	1.460	0.219	4.365	0.39	1.02	2.32	2.52	2.53	169

[a] For parameters explanation, see Experimental section.

Fig. 2. For subjects A, I, and L, it was impossible to find an acceptable solution, probably due to a very quick absorption, so that very poor information was available to describe the first absorption phenomenon. The estimated parameters for the other subjects are listed in Table III. The rate of drug absorption appears to be faster from the second intestinal segment

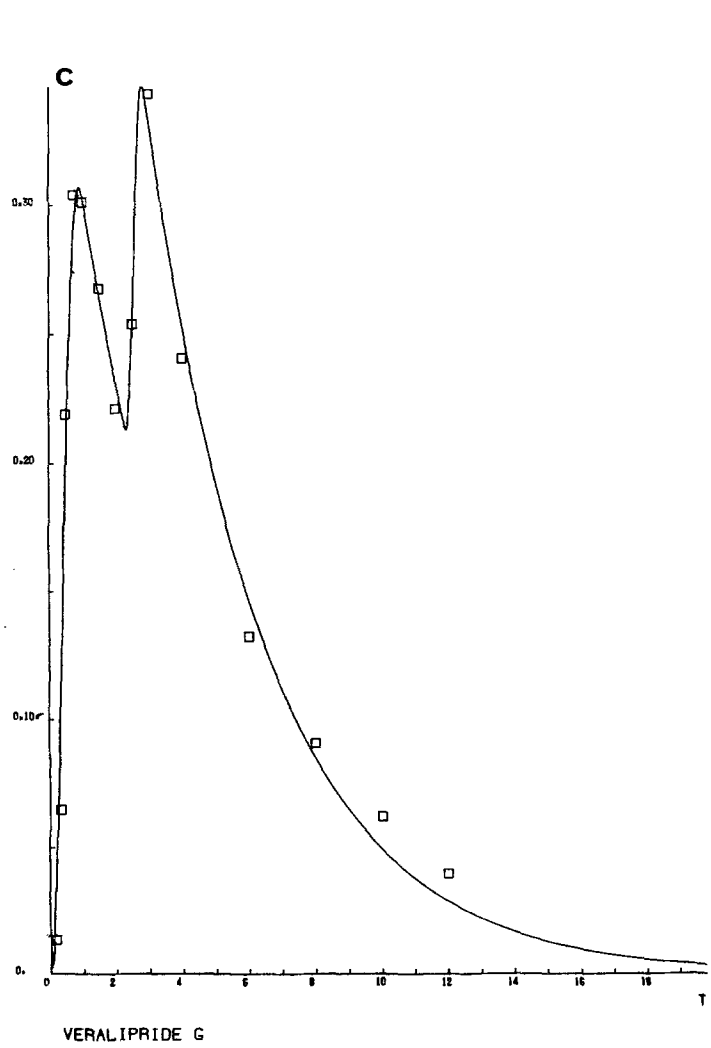

Fig. 2. Observed (□) and predicted (———) plasma profile of veralipride data for (a) subject G and (b) subject H, using the two-site absorption model, after the administration of an oral solution.

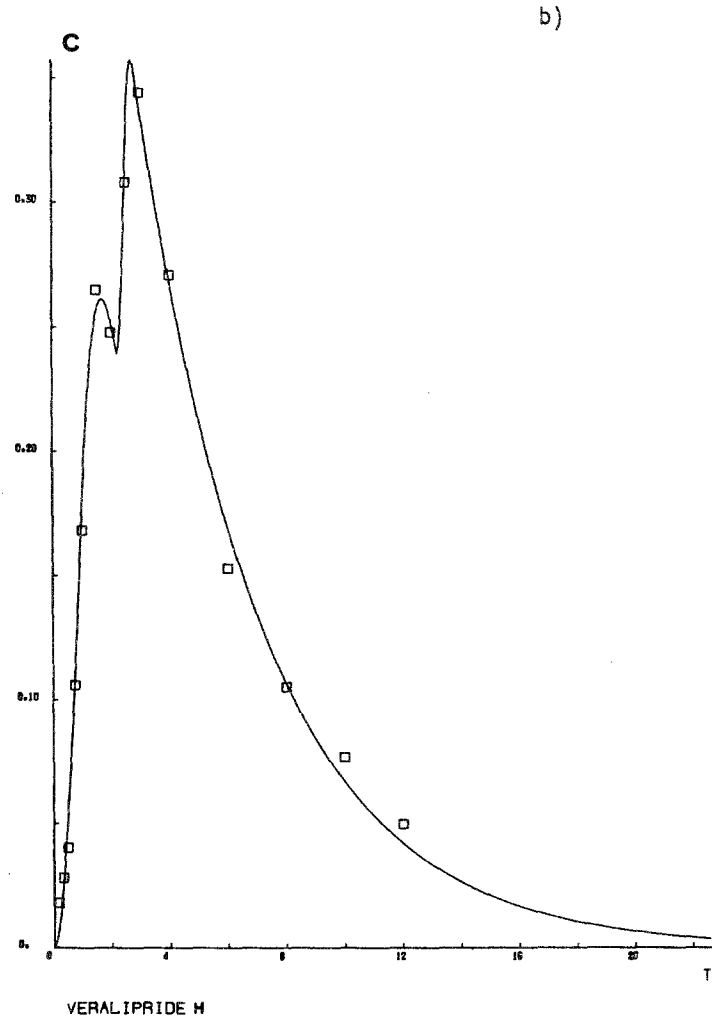

Fig. 2. Continued.

($k_3 = 5.85 \pm 0.64\ h^{-1}$ *vs.* $k_1 = 1.25 \pm 0.27\ h^{-1}$) and, for both, it seems that as soon as the drug is entirely within a segment, it begins to leave it ($T_2 - T_1$ and $T_5 - T_4$ are nearly zero) so that only a fraction of the administered dose is available for the penetration at any time.

Urine Samples Analysis

Examination of the cumulative excretion curves showed that the 5-day collection time was long enough to give a good approximation of the total

amount of the drug excreted at infinity. Then, the urinary excretion of unchanged drug accounts for about 50% of the administered dose after intravenous infusion; the results observed after oral intake roughly reflect the variations due to availability. The renal clearance of veralipride does not depend on drug administration and appears to be about 200 $mL \cdot min^{-1}$, which indicates a renal secretion phenomenon.

DISCUSSION

The plasma concentration profiles observed after the oral administration of the solution and the capsule are very different. They are quite regular after administration of the capsules, but a double peak is observed systematically after the solution intake. Thus, a classical pharmacokinetic interpretation was possible only for the former. In most cases, the second peak is higher than the first one. Such a type of observation is theoretically unlikely when a regular absorption associated with an enterohepatic recycling occurs, as only a part of the amount previously absorbed is available for reabsorption (perhaps except when high biliary first-pass effects occur). Furthermore, the first peak does not appear when the drug is administered as a capsule, the only peak occurring being observed at the same moment as the second one observed when the solution is administered. A possible explanation is that during the early time after ingestion, the drug is not available from the capsule to be absorbed across the gastrointestinal tract. In this regard, we assume that the first site of drug absorption probably corresponds to the stomach and/or to the upper part of the small intestine. Then we have applied this model for drug absorption and have obtained a satisfactory fit of the oral solution data, the secondary peak being very correctly characterized as shown in Fig. 2.

CONCLUSIONS

Irregular profiles of drug concentrations plasma curves are always difficult to describe. During the last few years, the importance of the enterohepatic recycling phenomenon has been pointed out but many physiological mechanisms may be involved. We feel that the present data support the hypothesis that a drug may be absorbed from different successive sites which can be modeled using the concept of the "absorption window" previously developed by Kubler (10).

APPENDIX

Let us denote by $A(t)$ the amount of drug in the body that is in the compartment I of the double-site absorption model (Fig. 1) and by $A_a(t)$

the amount of drug in the site of absorption, that is in the compartment II of the model. The differential equation system connected with this model is:

For $0 \leq t \leq T_1$

$$\begin{cases} \dfrac{dA}{dt} = k_1 A_a - k_2 A \\ \\ \dfrac{dA_a}{dt} = -k_1 A_a + u \end{cases} \quad \text{with } u = \frac{D}{T_1};\ A(0) = A_a(0) = 0$$

where D denotes the administered dose. Then

$$A(t) = \frac{D}{k_2 T_1 (k_2 - k_1)} [k_2 (1 - e^{-k_1 t}) - k_1 (1 - e^{-k_2 t})] \tag{A1}$$

For $T_1 \leq t \leq T_2$

$$\begin{cases} \dfrac{dA}{dt} = k_1 A_a - k_2 A \\ \\ \dfrac{dA_a}{dt} = -k_1 A_a \end{cases}$$

which leads to

$$A(t) = \frac{D}{k_2 T_1 (k_2 - k_1)} [k_2\, e^{-k_1 t} (e^{k_1 T_1} - 1) - k_1 e^{-k_2 t} (e^{k_2 T_1} - 1)] \tag{A2}$$

For $T_2 \leq t \leq T_2 + T_1$

$$\begin{cases} \dfrac{dA}{dt} = k_1 A_a - k_2 A \\ \\ \dfrac{dA_a}{dt} = -k_1 A_a - \alpha \end{cases}$$

α being a positive and constant rate which may be obtained as either the amount of drug leaving the segment divided by the time over which it empties; or as the boundary condition $A_a(T_1 + T_2) = 0$.

Whatever the process we obtain $\alpha = u\, e^{-k_1 T_2}$ so that

$$A(t) = \frac{-D}{k_2 T_1 (k_2 - k_1)} \times [k_1\, e^{-k_2 t} (e^{k_2 T_1} + e^{-(k_1 - k_2) T_2} - 1) - k_2\, e^{-k_1 (t - T_1)} - (k_1 - k_2)\, e^{-k_1 T_2}] \tag{A3}$$

and

$$A_a(t) = \frac{u}{k_1}[e^{-k_1(t-T_1)} - e^{-k_1 T_2}]$$

At Time $T_1 + T_2$

The amount of drug unabsorbed in the first segment and reaching the second can be estimated as follows:

$$A_{a,1} = D - k_1 \int_0^{T_1+T_2} A_a(t)\, dt = A_a(T_2) - k_1 \int_{T_2}^{T_2+T_1} A_a(t)\, dt.$$

The last integral can be calculated from

$$\int_{T_2}^{T_2+T_1} \left(\frac{dA_a}{dt}\right) dt = A_a(T_2+T_1) - A_a(T_2) = -k_1 \int_{T_2}^{T_2+T_1} A_a(t)\, dt - uT_1\, e^{-k_1 T_2}$$

which leads to $A_{a,1} = D\, e^{-k_1 T_2}$. (A4)

For $T_2 + T_1 \leq t \leq T_3$

$A(t) = A(T_1 + T_2)\, e^{-k_2(t-T_1-T_2)}$, thus:

$$A(t) = \frac{k_1 D}{k_2 T_1 (k_1 - k_2)}\, e^{-k_2 t}(e^{k_2 T_1} - 1)(1 - e^{-(k_1-k_2)T_2}) \tag{A5}$$

For $T_3 \leq t \leq T_4$

$A_a(t)$ also denotes the amount of drug in the second site of absorption, thus $A_a(T_3) = 0$ and $A(T_3)$ given by Eq. (5).

$$\begin{cases} \dfrac{dA}{dt} = k_3 A_a - k_2 A \\ \dfrac{dA_a}{dt} = -k_3 A_a + u_1 \end{cases}$$

where $u_1 = A_{a,1}/(T_4 - T_3)$ corresponds to the rate of the drug crossing the second segment of drug absorption.

Thus:

$$A(t) = \left[A(T_3) + \frac{k_3 u_1}{k_2(k_2 - k_3)}\right] e^{-k_2(t-T_3)} + \frac{u_1}{k_2} - \frac{u_1}{k_2 - k_3}\, e^{-k_3(t-T_3)} \tag{A6}$$

For $T_4 \leq t \leq T_5$

$$\begin{cases} \dfrac{dA}{dt} = k_3 A_a - k_2 A \\ \dfrac{dA_a}{dt} = -k_3 A_a \end{cases}$$

which leads to

$$A(t) = \left[A(T_4) - \frac{k_3 A_a(T_4)}{k_2 - k_3} \right] e^{-k_2(t-T_4)} + \frac{k_3 A_a(T_4)}{k_2 - k_3} e^{-k_3(t-T_4)} \tag{A7}$$

and

$$A_a(T_4) = \frac{u_1}{k_3}[1 - e^{-k_3(T_4 - T_3)}] \tag{A8}$$

For $T_5 \leq t \leq T_5 + T_4 - T_3$

With a rate fulfilling the boundary condition $A_a(T_5 + T_4 - T_3) = 0$ the system becomes

$$\begin{cases} \dfrac{dA}{dt} = k_3 A_a - k_2 A \\ \dfrac{dA_a}{dt} = -k_3 A_a - u_1 \, e^{-k_3(T_5 - T_3)} \end{cases}$$

This gives

$$A(t) = \left[A(T_5) + \frac{u_1}{k_2} e^{-k_3(T_5 - T_3)} - \frac{u_1}{k_2 - k_3} e^{-k_3(T_5 - T_4)} \right] e^{-k_2(t-T_5)}$$

$$+ \frac{u_1}{k_2 - k_3} e^{-k_3(t-T_4)} - \frac{u_1}{k_2} e^{-k_3(T_5 - T_3)} \tag{A9}$$

and

$$A_a(t) = \frac{u_1}{k_3}[e^{-k_3(t-T_4)} - e^{-k_3(T_5 - T_3)}]$$

For $t \geq T_5 + T_4 - T_3$

No more drug reaches compartment I so that nothing else can happen but elimination from the body:

$$A(t) = A(T_5 + T_4 - T_3) \, e^{-k_2(t - T_5 - T_4 + T_3)} \tag{A10}$$

Remark: Area Under the Amount of Drug Curves (AUAC)

The area under the amount of drug curves, from time 0 to infinity, is given by

$$AUAC = \int_0^\infty A(t)\,dt = \frac{1}{k_2}[D(1 - e^{-k_1 T_2}) + A_{a,1}(1 - e^{-k_3(T_5 - T_3)})] \quad \text{(A11)}$$

Thus, as $A_{a,1} = D\,e^{-k_1 T_2}$, it yields:

$$AUAC = \frac{D}{k_2}[1 - e^{-k_1 T_2 - k_3(T_5 - T_3)}] \quad \text{(A12)}$$

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