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Research Papers

PHARMACOKINETIC PROFILE OF ORAL DIGOXIN IN HEALTHY VOLUNTEERS

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SUMMARY

Healthy volunteers were dosed with digoxin tablets. Blood and urine samples were taken following an established protocol, and were assayed using Lanoxitest γ radioimmunoassay. Blood and urine data were fitted simultaneously to both 3 and 4 exponential functions of the type $(Qe^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t})$ and $(Qe^{-k_a t} + Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\pi t})$. The relevant mathematics for both procedures have been defined. The non-linear least-squares-fitting programmes used were NAG Subroutine Library and NONLIN. Both indicated that the kinetics of oral digoxin were best represented by a classical two-compartment linear model.

INTRODUCTION

Sumner et al. (1976) proposed a three-compartment open kinetic model as being the model most consistent with blood, urinary and faecal data following intravenous administration of tritiated digoxin. The present investigation was made to determine whether oral dosing with digoxin in healthy volunteers was best represented by a two- or a three-compartment model (Fig. 1a, b).

MATERIALS AND METHODS

Four healthy volunteers were dosed with 3 X 0.25 mg digoxin (Lanoxin) tablets. Blood and urine samples were collected at intervals over 6 days.

The samples were assayed using Lanoxitest γ radioimmunoassay kits and the unknown concentrations processed using a Hewlett-Packard model 9810A programmable calculator, fitted with 2K memory store. A model 9863A tape reader connected to the calculator was user-programmed to receive and transmit signals in ASCII Level 8 code. These

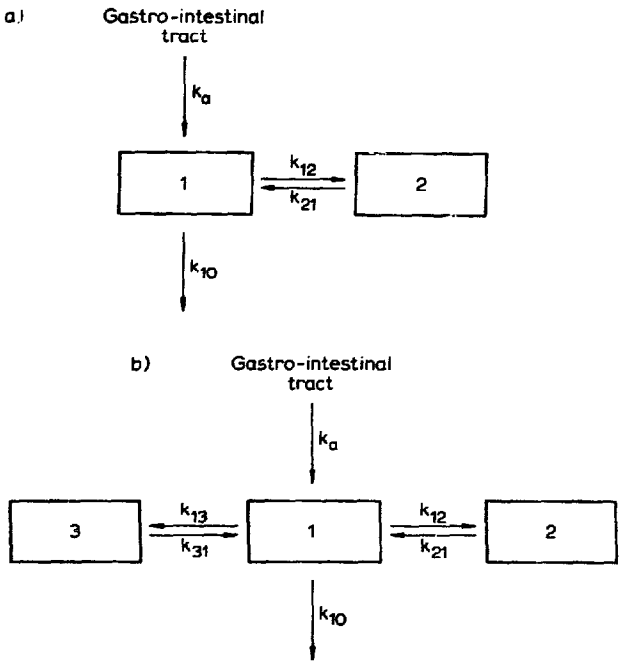

Fig. 1. a: two-compartment open kinetic model representing absorption, distribution and elimination of digoxin. All rate constants are first order. Compartment 1 represents the central compartment; compartment 2 represents a peripheral compartment. b: three-compartment open kinetic model representing absorption, distribution and elimination of digoxin. All rate constants are first order. Compartment 1 represents the central compartment; compartment 2 represents a shallow compartment; compartment 3 represents a deeper compartment.

signals arose from a logic circuit built into an LKB Wallac gamma counter and were punched on a standard ASR teleprinter punch. An X-Y plotter connected on-line to the calculator provided a visual linear display of the graphs generated. The linear display, as against the standard curve, was generated by performing a logit transformation (Rodbard and Lewald, 1970; Morgan, 1976).

The serum creatinine levels were determined on day one prior to dosing and day eight after dosing. This information was used to estimate creatinine clearance using a computer programme devised by Mawer (1976).

MATHEMATICS AND DATA-FITTING

Let D be the dose administered;
F be the fraction absorbed;
$A_1(t)$
$A_2(t)$
$A_3(t)$ be the amounts in each compartment at time t; and
k_a, k_{12}, k_{21}, k_{13}, k_{31}, k_{10} be the rate constants as in Fig. 1.

Then

$$\frac{dA_1}{dt} = FDk_a e^{-k_a t} + k_{21}A_2 + k_{31}A_3 - (k_{12} + k_{13})A_1 - k_{10}A_1$$

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

$$\frac{dA_3}{dt} = k_{13}A_1 - k_{31}A_3 .$$

These equations may be solved by the Laplace transform technique (Wagner 1975). Let

$$a_i(s) = \int_0^\infty A_i(t)e^{-st}dt \qquad (i = 1, 2, 3)$$

and taking $A_1(0) = A_2(0) = A_3(0) = 0$, then

$$a_1 = \frac{FDk_a(s + k_{21})(s + k_{31})}{(s + k_a)(s + \alpha)(s + \beta)(s + \pi)}$$

where

$$\alpha + \beta + \pi = k_{31} + k_{21} + k_{12} + k_{13} + k_{10}$$

$$\beta\pi + \pi\alpha + \alpha\beta = k_{21}k_{31} + k_{21}k_{13} + k_{21}k_{10} + k_{31}k_{12} + k_{31}k_{10}$$

$$\alpha\beta\pi = k_{21}k_{31}k_{10} .$$

Also,

$$a_2 = \frac{FDkak_{12}(s + k_{31})}{(s + k_a)(s + \alpha)(s + \beta)(s + \pi)}$$

and

$$a_3 = \frac{FDk_ak_{13}(s + k_{21})}{(s + k_a)(s + \alpha)(s + \beta)(s + \pi)}$$

Taking the inverse transform:

$$A_1 = FDk_a e^{-k_a t}\frac{(k_{21} - k_a)(k_{31} - k_a)}{(\alpha - k_a)(\beta - k_a)(\pi - k_a)}$$

$$+ FDk_a e^{-\alpha t}\frac{(k_{21} - \alpha)(k_{31} - \alpha)}{(k_a - \alpha)(\beta - \alpha)(\pi - \alpha)}$$

$$+ FDk_a e^{-\beta t}\frac{(k_{21} - \beta)(k_{31} - \beta)}{(k_a - \beta)(\alpha - \beta)(\pi - \beta)}$$

$$+ FDk_a e^{-\pi t}\frac{(k_{21} - \pi)(k_{31} - \pi)}{(k_a - \pi)(\alpha - \pi)(\beta - \pi)}$$

$$A_2 = FDk_a e^{-k_a t} \frac{k_{12}(k_{31} - k_a)}{(\alpha - k_a)(\beta - k_a)(\pi - k_a)}$$

$$+ FDk_a e^{-\alpha t} \frac{k_{12}(k_{31} - \alpha)}{(k_a - \alpha)(\beta - \alpha)(\pi - \alpha)}$$

$$+ FDk_a e^{-\beta t} \frac{k_{12}(k_{31} - \beta)}{(k_a - \beta)(\alpha - \beta)(\pi - \beta)}$$

$$+ FDk_a e^{-\pi t} \frac{k_{12}(k_{31} - \pi)}{(k_a - \pi)(\alpha - \pi)(\beta - \pi)}$$

$$A_3 = FDk_a e^{-k_a t} \frac{(k_{21} - k_a)\, k_{13}}{(\alpha - k_a)(\beta - k_a)(\pi - k_a)}$$

$$+ FDk_a e^{-\alpha t} \frac{(k_{21} - \alpha)\, k_{13}}{(k_a - \alpha)(\beta - \alpha)(\pi - \alpha)}$$

$$+ FDk_a e^{-\beta t} \frac{(k_{21} - \beta)\, k_{13}}{(k_a - \beta)(\alpha - \beta)(\pi - \beta)}$$

$$+ FDk_a e^{-\pi t} \frac{(k_{21} - \pi)\, k_{13}}{(k_a - \pi)(\alpha - \pi)(\beta - \pi)}$$

The available data points relate to two functions both derivable from $A_1(t)$. The first set of points represents the concentration in the main compartment, $C_1(t)$, defined by:

$$C_1(t) = A_1(t)/V_1$$

where V_1 is the apparent volume of the main compartment. The second set of points represents the accumulated urine data. The rate of transfer is:

$$\frac{dX_u}{dt} = k_e A_1$$

where $0 \leqslant k_e \leqslant k_{10}$, since this is only one of the elimination processes covered by k_{10}. Therefore the accumulated amount is:

$$X_u(t) = k_e \int^t A_1(t)\, dt = k_e V_1 \int^t C_1(t)\, dt$$

with the constant of integration chosen so that $X_u(0) = 0$.
Thus, the concentration data is fitted to the equation:

$$C_1(t) = \frac{FD}{V_1} k_a \left[\frac{(k_{21} - k_a)(k_{31} - k_a)}{(\alpha - k_a)(\beta - k_a)(\pi - k_a)} e^{-k_a t} \right.$$

$$\left. + \frac{(k_{21} - \alpha)(k_{31} - \alpha)}{(k_a - \alpha)(\beta - \alpha)(\pi - \alpha)} e^{-\alpha t} \right.$$

$$+\frac{(k_{21}-\beta)(k_{31}-\beta)}{(k_a-\beta)(\alpha-\beta)(\pi-\beta)}e^{-\beta t}$$

$$+\frac{(k_{21}-\pi)(k_{31}-\pi)}{(k_a-\pi)(\alpha-\pi)(\beta-\pi)}e^{-\pi t}\Bigg]$$

and simultaneously the accumulated urine data is fitted to:

$$X_u(t)=\frac{FD}{V_1}\,k_eV_1k_a\Bigg[\frac{(k_{21}-k_a)(k_{31}-k_a)}{(\alpha-k_a)(\beta-k_a)(\pi-k_a)}\,\frac{1-e^{-k_at}}{k_a}$$

$$+\frac{(k_{21}-\alpha)(k_{31}-\alpha)}{(k_a-\alpha)(\beta-\alpha)(\pi-\alpha)}\,\frac{1-e^{-\alpha t}}{\alpha}$$

$$+\frac{(k_{21}-\beta)(k_{31}-\beta)}{(k_a-\beta)(\alpha-\beta)(\pi-\beta)}\,\frac{1-e^{-\beta t}}{\beta}$$

$$+\frac{(k_{21}-\pi)(k_{31}-\pi)}{(k_a-\pi)(\alpha-\pi)(\beta-\pi)}\,\frac{1-e^{-\pi t}}{\pi}\Bigg]$$

These equations contain 8 independently variable parameters, which are chosen to be:

$$\frac{FD}{V_1}\,;\,k_a\,;\,k_{21}\,;\,k_{31}\,;\,\alpha\,;\,\beta\,;\,\pi\,;\,k_eV_1\,.$$

After optimization, the remaining 3 true parameters: k_{10}, k_{12} and k_{13}, may be recovered by inverting the equations which defined α, β and π:

$$k_{10}=\frac{\alpha\beta\pi}{k_{21}k_{31}}$$

$$k_{12}+k_{13}=\alpha+\beta+\pi-k_{10}-k_{21}-k_{31}$$

$$k_{31}k_{12}+k_{21}k_{13}=\beta\pi+\pi\alpha+\alpha\beta-k_{21}k_{31}-k_{21}k_{10}-k_{31}k_{10}$$

The mathematics for a two-compartment model is a special case of the above with $k_{31} = k_{13} = 0$, which implies also $\pi = 0$. There are then 3 exponential terms in the functions for $A_1(t)$, $C_1(t)$, and $X_u(t)$; and there are 6 independently variable parameters in the fit.

Before fitting, the urine data was rescaled so that the values were of the same order of magnitude as the concentration data values, thus ensuring that the two functions received approximately equal emphasis in the fitting process.

The data fitting process may be simplified by noting that the equations for $C_1(t)$ and $X_u(t)$ are linear in the functions

$$b_1=\frac{FD}{V_1}\,k_{21}k_{31}$$

$$b_2 = \frac{FD}{V_1}(k_{21} + k_{31})$$

$$b_3 = \frac{FD}{V_1}$$

$$b_4 = \frac{1}{k_e V_1}$$

and that this entire dependence on the parameters $\frac{FD}{V_1}$, k_{21}, k_{31} and $k_e V_1$ is thereby accounted for. Thus, we need subject only the 4 remaining parameters, k_a, α, β, and π, to full non-linear minimization procedures. That is, for any set values of (k_a, α, β, π) chosen by the non-linear minimization procedure, we may *not* evaluate the sum of squares of residuals straightaway; but rather we may reduce the equations for $C_1(t)$ and λ_u to the form:

$$C_1(t) = b_1 U(t) + b_2 V(t) + b_3 W(t)$$

$$b_4 X_u(t) = b_1 u(t) + b_2 v(t) + b_3 w(t)$$

where, U, V, W, u, v, w, are functions of (t) only (for fixed k_a, α, β, π). We may then determine the optional values of b_1, b_2, b_3, b_4 by a *linear* least-squares fit to the data-points, and hence, the least sum of squares of residuals. (Note: the 'mix' of C_1 and X_u used to find the linear parameters (per above) differs from the mix used to find the non-linear parameters in that X_u is multiplied by b_4 here. This is unlikely to give rise to serious trouble.)

The experimental data were fitted using non-linear least-squares regression analysis. The programmes utilized were Numerical Algorithms Group Mark 4 library, and NONLIN (Metzler, 1969). The Numerical Algotithms Group Mark 4 library was used initially as part of an on-line facility for rapid evaluation of parameters. The final parameters were then fitted using the NONLIN programme which gave a graphical print-out.

However, this system which gave the best fit could not be related back to the model as certain rate constants became negative. This was caused by convergence to a local minimum on the least-squares surface rather than the true minimum. This phenomenon was corrected by 'mapping' the least-squares surface (Wagner, 1975). Numerous minima were found and investigated; the rate constants were further constrained by keeping them positive and the programme extended to indicate the amount of drug in each compartment at a specified time.

RESULTS

Table 1 lists the best values of pharmacokinetic parameters obtained, together with the total sum of square deviations. The sum of squares obtained when fitting data to a three-compartment model were always lower than those obtained with a two-compartment model. However, the three compartment models were always invalid as one or more rate constants were negative. It is indicated, therefore, that with oral dosing a two-

TABLE 1

THE BEST VALUES OF PHARMACOKINETIC PARAMETERS OBTAINED, TOGETHER WITH THE TOTAL SUM OF SQUARES DEVIATIONS FOR BOTH THE TWO AND THREE-COMPARTMENT MODEL WITH FIRST ORDER ABSORPTION

Healthy volunteer	Model	FD/V_1	k_{21}	k_{31}	π	α	β	k_a	k_eV_1	Total sum of squares deviations for both curves
NM	2-compartment model with first order absorption	6.092	0.182	–	–	0.013	0.936	0.961	0.061	17.25
NM	3-compartment model with first order absorption [a]	2.372	4.599	0.07216	0.9594	1.042	0.1191	1.402	0.7578	10.30943
JE	2-compartment model with first order absorption [a]	3.058	3.423	–	–	0.0244	4.865	5.392	0.04679	39.82578
JE	3-compartment model with first order absorption [a]	3.502	5.740	0.05419	0.8616	2.937	0.001103	3.324	0.7585	8.425244
DH	2-compartment model with first order absorption	7.93	0.077	–	–	0.014	0.7792	0.766	0.072	5.53
DH	3-compartment model with first order absorption [a]	1.651	9.604	0.08166	1.284	1.266	0.01394	1.266	0.7065	2.19078
PC	2-compartment model with first order absorption	8.906	0.065	–	–	0.014	0.736	0.987	0.073	8.54
PC	3-compartment model with first order absorption [a]	2.256	7.713	0.06837	0.4554	2.670	0.01365	2.900	0.5918	5.925765

[a] Invalid models due to one or more of the rate constants k_{12}, k_{13}, and k_{10} being negative.

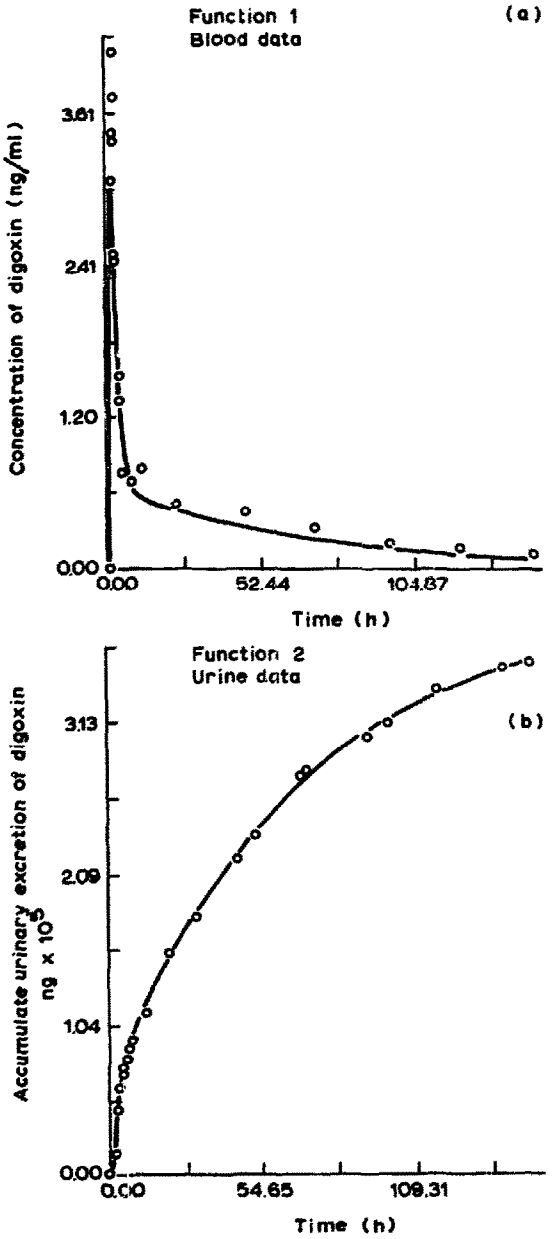

Fig. 2. Data-fitting to a two-compartment model with first order absorption for volunteer DH. a: serum concentration of digoxin against time. b: accumulated urinary excretion of digoxin. (o, experimental observations; – fitted model)

compartment linear model gives the best fit to the data (Fig. 2). The values of the rate constants for a two-compartment model are given in Table 2.

Data fitting in the two older volunteers with the lower estimated values of creatinine clearance (Table 3) gave a better fit. Table 4 indicates the time of peak levels of drug obtained in each compartment.

TABLE 2

RATE CONSTANTS FOR THE VOLUNTEERS NM, PC AND DH FOR TWO-COMPARTMENT MODELS WITH FIRST ORDER ABSORPTION

Healthy volunteer	FD/V_1	k_eV_1	k_{21}	k_{10}	k_{12}	k_a
NM	6.092	0.061	0.182	0.070	0.697	0.961
JE	–	–	–	–	–	–
PC	8.906	0.073	0.065	0.155	0.529	0.987
DH	7.931	0.072	0.076	0.145	0.571	0.766

TABLE 3

RENAL FUNCTION INDICATED AS ESTIMATED CREATININE CLEARANCE FROM THE PARAMETERS AGE, SEX, WEIGHT AND SERUM CREATININE ON DAY 1 AND DAY 8 AFTER DOSING, USING A PROGRAMME BY MAWER (1976)

Healthy volunteer	Age	Sex	Weight (kg)	Serum creatinine (μmol/l)		Estimated creatinine clearance (ml/min)
				Day 1	Day 8	
NM	25	M	78	70	80	141
JE	22	M	71	80	80	132
PC	32	M	61	90	90	92
DH	33	M	67	80	80	113

TABLE 4

THE TIMES AT WHICH THE MAXIMUM PROPORTION OF DRUG APPEARED IN EACH COMPARTMENT FOR VOLUNTEERS NM, PC AND DH

Healthy volunteer	Compartment 1		Compartment 2	
	Time (hr)	Maximum proportion of drug	Time (hr)	Maximum proportion of drug
NM	1.200	0.459	6.670	0.690
JE	–	–	–	–
PC	1.250	0.442	7.050	0.661
DH	1.520	0.386	7.270	0.667

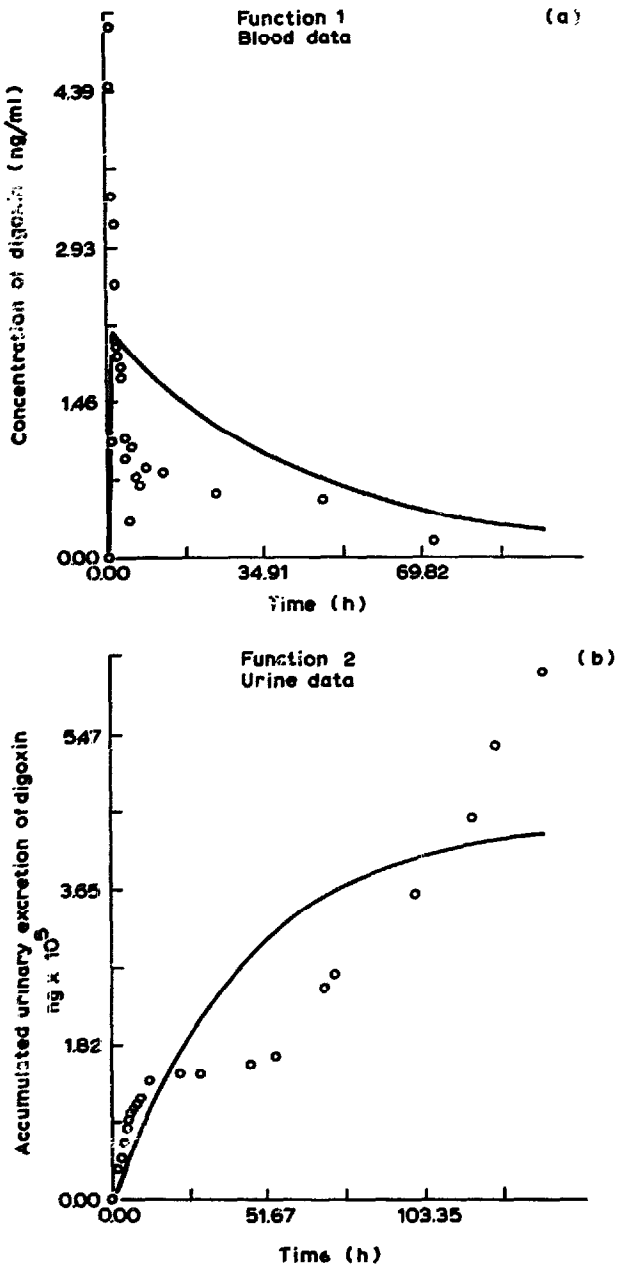

Fig. 3. Attempted data-fitting to a two-compartment model with first order absorption for volunteer JE. a: serum concentration of digoxin against time. b: accumulated urinary excretion of digoxin. (o, experimental observations; – fitted model)

Fig. 3 represents the best attempt at fitting the data to a two-compartment model, but it was considered unsatisfactory due to the relatively large value of sum of squares deviations (Table 1). The S-shaped nature of the curve for cumulative urinary excretion

(Fig. 3b) was consistent with the unusual results obtained for serum concentration of digoxin (Fig. 3a).

DISCUSSION

Estimation of serum digoxin levels

Kubasik et al. (1976) evaluated the sensitivity of 12 commercially available digoxin radioimmunoassay kits. They concluded that the Lanoxitest kit, as used in this present study, was capable of distinguishing between 0.1 ng/ml and a zero level of digoxin, and between various digoxin levels from 0.1 through 0.5 ng/ml. Also, the use of logit transformation as described by Rodbard and Lewald (1970), rather than manual drawing of a standard curve, increased the accuracy of calculating unknown concentrations at low levels.

Estimation of creatinine clearance

The computer programme of Mawer (1976) took into account the age, sex and weight of each volunteer, together with any change in serum creatinine levels between consecutive measurements when estimating creatinine clearance (see Table 3). While not being as accurate a value as would be obtained by direct measurement of creatinine clearance, in healthy individuals with a relatively stable serum creatinine level such an estimation would have given a reasonable indication of glomerular filtration rate.

Compartmental modelling

Following intravenous administration, Reuning et al. (1973) proposed that the pharmacokinetics of tritiated digoxin was best represented by a two-compartment open model. However, other workers (Doherty and Perkins, 1962; Doherty et al., 1967; Kramer et al., 1973; Sumner et al., 1976) have presented evidence to suggest that a three-compartment open model better represents data obtained following intravenous administration of tritiated digoxin.

Because of difficulties of interpretation posed by the oral data, due to the exchange of the tritium label and the breakdown of [12α-^{3}H]digoxin in the acid environment of the stomach, Sumner et al. (1976) only fitted intravenous data to a three-compartment model. However, the present work indicated that the classical two-compartment linear model, as shown in Fig. 1a, best represents the pharmacokinetics of oral digoxin. A possible explanation of the apparent discrepancy between the two-compartment model proposed in this present work for oral dosing and the three-compartment model proposed by Sumner et al. (1976) for intravenous dosing, is that with oral absorption k_a is probably a hybrid rate constant that defines both the absorption and initial phase of rapid distribution of digoxin.

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