Pharmacokinetics of phenylpropanolamine in humans after a single-dose study

R. Dowse, J.M. Haigh and I. Kanfer

School of Pharmaceutical Sciences, Rhodes University, Grahamstown (South Africa)

Summary

The pharmacokinetics of phenylpropanolamine have been studied in healthy human volunteers following the oral administration of an aqueous solution of the drug (50 mg/200 ml). Blood and urine samples collected throughout the trial were assayed using HPLC with UV detection. The drug was shown to be rapidly absorbed with a mean t_{max} of 1.47 ± 0.49 h and a mean elimination half-life of 4.0 ± 0.5 h. Phenylpropanolamine is predominantly excreted via the kidney with a mean renal clearance of 0.646 ± 0.089 liter/kg/h and $90.2 \pm 1.7\%$ excreted unchanged in the urine. The data were not well described using conventional one or two body compartment models. However, the incorporation of a discontinuous absorption phase into the models resulted in an improved overall fit with better characterisation of the absorption phase.

Introduction

Phenylpropanolamine (PPA), a sympatho-mimetic amine, is widely used as a nasal decongestant and is a component of many proprietary cold preparations. In larger doses, PPA is used as an appetite suppressant and is one of the most popular over-the-counter appetite suppressants in the U.S.A. However, over the past few years, PPA has been the focus of much controversy due to its reported undesirable side effects and the potential of this drug for abuse. Many reports and letters have appeared in the literature condemning the use of PPA (King, 1979; Horowitz, et al., 1980;

Bernstein and Diskant, 1982; Greenwood, 1983; McDowell and LeBlanc, 1985).

Despite its extensive use, a literature survey revealed a distinct paucity of information concerning the kinetics of absorption and disposition of PPA (Dowse, 1984). The absence of such pharmacokinetic data can be attributed to the lack of an analytical method sensitive enough to determine the low concentrations of PPA found in plasma. Previous kinetic studies were limited to the determination of PPA in urine only (Heimlich et al., 1961; Beckett and Wilkinson, 1965; Wilkinson and Beckett, 1968a and b) and the only pharmacokinetic parameters, half-life and absorption rate reported to date, have been based on these urine data.

A pharmacokinetic study of PPA using both blood and urine data described the steady-state

Correspondence: I. Kanfer, School of Pharmaceutical Sciences, Rhodes University, Grahamstown 6140, South Africa.

kinetics of the drug administered in a sustained-release formulation (Lönnerholm et al., 1984). The apparent mean half-life was found to be 5.6 h. Values were also calculated for mean steady-state concentration, area under the plasma concentration–time curve, apparent volume of distribution and renal clearance.

The present study was undertaken to examine the absorption and disposition of PPA in humans following the administration of an aqueous solution of the drug. A newly developed, sensitive, specific HPLC assay (Dowse et al., 1983) was used to determine serum and urine concentrations of the drug.

Materials and Methods

Trial design

Six healthy volunteers who were non-smokers participated in the trial. They ranged in age from 21 to 28 years and weighed between 54 and 79 kg. Volunteers were chosen on the basis of interview, physical health and standard laboratory tests which included haematology, blood chemistry and urinalysis. Informed consent was obtained from each subject. Following an overnight fast, each subject received a test dose. A standardized breakfast was served 2 h after the start of the trial.

Trial schedule: 50 mg PPA hydrochloride (PPA.HCl) dissolved in 200 ml of water was administered to each of 6 subjects. Blood samples were drawn before dosing and at 10-min intervals for the first h, then at 1, $1\frac{1}{2}$, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 24 h after administration of the drug. Serum was separated by centrifugation and urine samples were collected throughout the trial. All samples were stored at $-20°C$ until analysis.

Analytical method

Serum and urine concentrations of PPA.HCl were determined by HPLC using direct UV detection. The method involved chloroform extraction at a basic pH and a single back-extraction into 5% v/v acetic acid (Dowse et al., 1983). An aliquot of the acidic extract was injected directly onto the column. The limit of detection was 25 ng/ml at which the coefficient of variation was 5.2%.

Calculation of bioavailability parameters

Maximum PPA serum concentrations, C_{max}, and the time to obtain this concentration, t_{max}, were determined from individual PPA serum concentration profiles. Area under the curve (AUC) data were calculated using the linear trapezoidal equation in the absorption phase and the log trapezoidal method in the postabsorption phase where the function declines monoexponentially. The terminal rate constant, K_{el}, was calculated from the terminal slope of a semilog plot of serum concentration vs time and the elimination half-life, $t_{\frac{1}{2}}$, was thus obtained.

The apparent volume of distribution, V, was estimated using the following equation, assuming $F = 1$:

$$V = \frac{F \cdot D}{AUC_\infty \cdot K_{el}} \tag{1}$$

where D is the dose in μg.

The percent of the dose excreted unchanged, $\%E$, was determined directly from urine data. The excretion rates were plotted against the serum concentrations at the mid-points of the excretion intervals and renal clearance was obtained from the slope of this line.

Modelling of data

Individual serum concentration–time data were fitted by non-linear regression analysis to various models (see Fig. 1) using the program NONLIN (Metzler, 1974) with equal weighting to the data points.
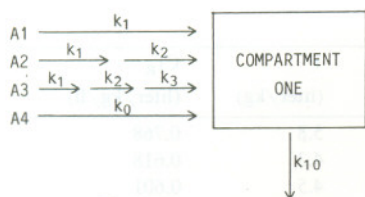
Eqn. 2 describes a one-body compartment model (1BCM) with first order absorption and Eqn. 3 characterises a 2BCM with first order absorption and elimination solely from the central compartment.

$$\frac{dC}{dt} = k_{a_x}\frac{D}{V}e^{-k_{a_x}(t-t_0)} - K_{10}C_1 \tag{2}$$

$$\frac{dC_1}{dt} = k_{a_x}\frac{D}{V}e^{-k_{a_x}(t-t_0)} + K_{21}\frac{A_2}{V} - K_{12}C_1 - K_{10}C_1 \tag{3}$$

The interpretation of PPA absorption as zero order

MODEL A

A1 →k_1→

A2 →k_1→ →k_2→

A3 →k_1→ →k_2→ →k_3→

A4 →k_0→

COMPARTMENT ONE

↓k_{10}

MODEL B

B1 →k_1→

B2 →k_1→ →k_2→

B3 →k_1→ →k_2→ →k_3→

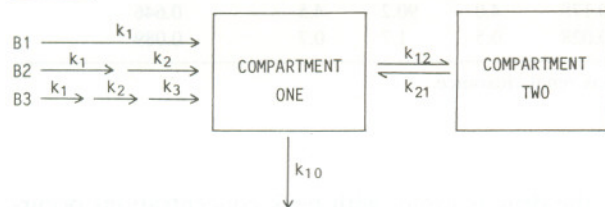COMPARTMENT ONE →k_{12}→ ←k_{21}← COMPARTMENT TWO

↓k_{10}

Fig. 1. Pharmacokinetic models for phenylpropanolamine.

input was assessed by fitting the data to the following equation:

$$C = \frac{k_0(e^{K_{10}T} - 1)\, e^{-K_{10}t}}{V K_{10}} \quad (4)$$

where

dC/dt = rate of change of drug concentration in the central compartment

k_{a_x} = first, second or third absorption rate constant

D = dose of the drug

V = volume of the central compartment

A_2 = amount of drug in the peripheral compartment

C_1 = concentration in the central compartment

K_{10} = elimination rate constant

K_{12} = first order rate constant for transfer of drug from the central to the peripheral compartment

K_{21} = first order rate constant for transfer of drug from the peripheral to the central compartment

t = time after drug administration

t_0 = lag time between drug administration and appearance of drug in the serum

k_0 = apparent zero order absorption rate constant

T = a constant corresponding to the absorption time, after absorption apparently ceases. (During absorption, T is a variable and equal to t)

The possibility of discontinuous absorption of PPA was investigated by modifying the differential equations describing the model to include 2 or 3 absorption rate constants (see Fig. 1). The times at which the absorption rates changed were estimated by studying the individual serum concentration–time profiles.

Goodness of fit was assessed by calculating the correlation coefficient for each set of observed and predicted data, and by visual observation of the curves. Akaike's Information Criterion (AIC) was used to select an appropriate model describing the experimental data (Yamaoka et al., 1978), with the equation having the minimum AIC being regarded as best characterising the data set.

$$AIC_j = n \ln Re_j + 2p \quad (5)$$

Where additional parameters were added to a model, the F ratio test (Boxenbaum et al., 1974) was applied to determine whether or not the weighted sums of squared deviations were sufficiently reduced to justify fitting with the additional parameters,

$$F = \left(\frac{Re_j - Re_k}{Re_k}\right) \times \left(\frac{n_k - p_k}{(n_j - p_j) - (n_k - p_k)}\right)$$

$$(6)$$

where n is the number of observations, p, the number of parameters, Re, the weighted sum of squared deviations and j and k represent the jth or k^{th} data set.

Results

Pharmacokinetic data

Table 1 summarises the pharmacokinetic data. Mean serum and urine profiles ($\pm$ S.D.) are depicted in Figs. 2 and 3, respectively. Absorption of

TABLE 1

Pharmacokinetic parameters for PPA

Subject	Weight (kg)	t_{max} (h)	C_{max} (ng/ml)	AUC_∞ (ng/ml · h)	K_{el} (h^{-1})	$t\frac{1}{2}$ (h)	%E	V (liter/kg)	Cl_R (liter/kg/h)
1	67	1.50	112.21	809.01	0.160	4.3	89.0	5.8	0.768
2	77	2.00	114.10	858.62	0.177	4.0	88.7	4.3	0.618
3	62	1.00	154.97	1 135.39	0.157	4.4	89.0	4.5	0.601
4	79	2.00	116.70	839.57	0.180	3.9	92.6	4.2	0.576
5	71	0.83	139.62	773.40	0.232	3.0	90.2	3.9	0.748
6	54	1.50	185.68	1 433.83	0.163	4.3	91.9	4.0	0.566
Mean	68	1.47	137.21	926.64	0.178	4.0	90.2	4.5	0.646
± S.D.	9	0.49	29.16	167.50	0.028	0.5	1.7	0.7	0.089

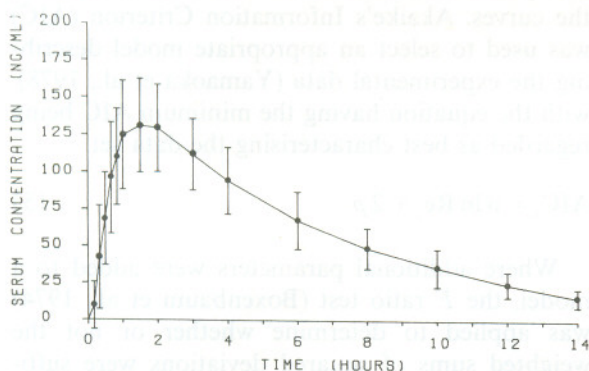%E is the percentage of unchanged drug excreted in the urine; Cl_R is renal clearance.

Fig. 2. Mean PPA serum concentrations (± S.D.) following the oral administration of a 50 mg aqueous solution of the drug.
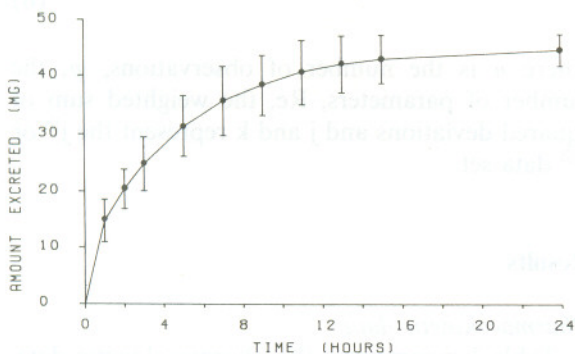

Fig. 3. Mean PPA urine excretion curve (± S.D.) following the oral administration of a 50 mg aqueous solution of the drug.

the drug is rapid, with peak concentrations occurring between 50 min and 2 h after ingestion, which agrees with the results of a previous study (Mason and Amick, 1981). Peak concentrations range from 112 ng/ml to 186 ng/ml.

The apparent volume of distribution is large, 4.5 ± 0.7 liter/kg, which would account for the low concentrations of PPA found in the serum. This rather high distribution volume indicated that PPA is extensively bound to extravascular sites. The tissue distribution in dogs 2 h after administration was found to be kidney > lung > liver > spleen > brain > heart > muscle > plasma > fat > CSF (Axelrod, 1953).

Half-life values were found to range between 3.0 and 4.4 h, similar to values calculated in previous urinary excretion studies (Heimlich et al., 1961; Wilkinson and Beckett, 1968a). PPA is reported to be completely absorbed, with approximately 90% of the unchanged drug being excreted in the urine in 24 h (Heimlich et al., 1961). In one study (Sinsheimer et al., 1973) only 4% was found as transformation products. The percent of unchanged PPA recovered from the urine ranged from 89 to 93% (Table 1), supporting the theory of complete absorption and negligible metabolism of the drug.

The relationship between renal clearance and serum concentration was determined under dynamic conditions, as serum concentrations of PPA were not at steady-state and changed rapidly. Large intra-individual differences between the

subjects in renal clearance occurred during the trials. The mean renal clearance of 0.646 liter/kg/h exceeds the glomerular filtration rate, indicating that a substantial proportion of the dose was eliminated by tubular secretion.

Flow rate and urine pH have been shown to have an effect on the clearance of certain drugs (Rowland and Tozer, 1980). Urine pH was monitored throughout the trial and was found to fluctuate between 5.5 and 7.5. Phenylpropanolamine, being a weak base with a pK_a of 9.4 (Kanfer et al., 1983), would not undergo significant tubular reabsorption at these pH values.

Modelling

The mean pharmacokinetic parameters from fitting the serum data to the various models are shown in Table 2. Both the 1BCM and 2BCM with first order absorption were unable to account for the rapid absorption phase and resulted in a large over-estimation of initial concentrations followed by an inability to attain the high peak concentrations (Figs. 4 and 5).

A rapid increase in drug concentration after oral administration followed by a fairly rapid decline is reported to be characteristic of zero order absorption (McNamara et al., 1978). Therefore a model incorporating zero order absorption was used in an attempt to improve characterisation of the absorption and immediate postabsorption phases. This resulted in a slight improvement of fit as indicated by the correlation coefficients which increased from a mean of 0.967 to 0.981, AIC values (Table 3) and visual observation (Fig. 4).
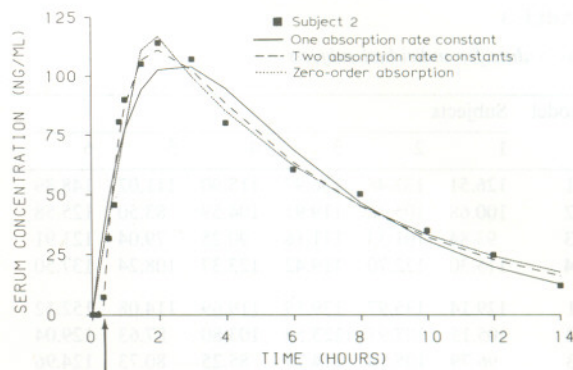

Fig. 4. Observed data for Subject 2 and computer-predicted fits to the 1BCM with one absorption rate constant, two absorption rate constants and zero order absorption. The arrow indicates the time chosen for the k_a to change in the 1BCM with two k_a's.
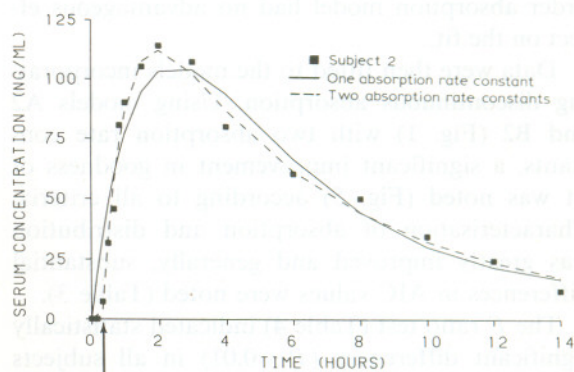

Fig. 5. Observed data for Subject 2 and computer-predicted fits to the 2BCM with one and two absorption rate constants. The arrow indicates the time chosen for the k_a to change in the 2BCM with two k_a's.

TABLE 2

Mean pharmacokinetic parameters of the 7 models

Model	k_{a_1} (h^{-1})	k_{a_2} (h^{-1})	k_{a_3} (h^{-1})	k_0 (μg/h)	V (liter)	K_{10} (h^{-1})	t_{lag} (h)	K_{12} (h^{-1})	K_{21} (h^{-1})	T (h)
A1	1.237				310.1	0.203	0.137			
A2	0.461	2.491			265.4	0.170	0.171			
A3	0.406	2.863	2.451		259.9	0.174	0.181			
A4				41 488.1	286.9	0.160				1.17
B1	0.918				240.9	0.217	0.209	0.197	0.379	
B2	0.432	2.251			227.9	0.192	0.163	0.360	1.692	
B3	0.382	3.007	2.023		257.5	0.199	0.207	0.275	1.766	

TABLE 3

AIC values for individual subjects

Model	Subjects					
	1	2	3	4	5	6
A1	126.51	132.48	136.97	115.90	111.02	148.89
A2	100.68	105.26	119.91	104.59	83.50	125.58
A3	93.84	101.33	111.16	90.25	79.04	121.91
A4	115.30	122.70	119.42	123.37	108.24	137.50
B1	129.14	135.97	139.19	119.69	114.08	152.12
B2	105.15	107.97	123.53	103.80	87.63	129.04
B3	96.79	105.14	114.79	85.25	80.73	124.96

However, on close inspection of individual data, the resulting curves were not well characterised. The inclusion of a lag-time parameter in the zero order absorption model had no advantageous effect on the fit.

Data were then fitted to the models incorporating discontinuous absorption. Using models A2 and B2 (Fig. 1) with two absorption rate constants, a significant improvement in goodness of fit was noted (Fig. 5) according to all criteria. Characterisation of absorption and distribution was greatly improved and generally, substantial differences in AIC values were noted (Table 3).

The F ratio test (Table 4) indicated statistically significant differences ($P < 0.01$) in all subjects between the models incorporating a single absorption rate constant and those characterised by discontinuous absorption.

A third absorption rate constant was then introduced and all individual data sets fitted to this model. However, although AIC values were lower,

TABLE 4

Results of statistical comparison of models using the F-ratio test

Models compared	Subjects					
	1	2	3	4	5	6
A1/A2	51.62 *	57.31 *	25.21 *	14.27 *	58.62 *	42.53 *
A2/A3	7.38	4.49	9.58	1.78	4.97	4.25
B1/B2	36.68 *	49.72 *	18.15 *	18.53 *	44.28 *	34.14 *
B2/B3	7.29	0.35	7.65	20.89 *	5.95	3.70

* Statistically significant difference ($P < 0.01$).

a statistically significant improvement with this model, as indicated by the F ratio test, was observed in only one subject (Subject 4).

Discussion

A possible problem using equal weighting in non-linear least squares regression is that too little emphasis will be placed on very low concentrations if the data extend over a wide range of concentrations. Data in this study were initially fitted using equal weighting and compared to results obtained using weighting done according to the reciprocals of the observations. No improvement of fit either to the high or low concentrations was observed, and parameter estimates using equal weighting were in closer agreement to values calculated using non-compartmental methods.

Discontinuous absorption processes in relation to linear pharmacokinetic models have been reported by Süverkrüp (1979) and Zimmerman (1983). Zimmerman used a system of differential equations in which sequential sets of equations were used to describe the absorption profile from time zero to infinity. The usefulness of these equations was demonstrated by obtaining excellent fits for some unusual absorption profiles of griseofulvin (Bates and Carrigan, 1975) and sulfisoxazole (Kaplan et al., 1972). With both of these drugs, previous, less successful attempts had been made to characterise the absorption using zero order input.

Excellent characterisation of the absorption phase resulted from the use of a biphasic, discontinuous absorption model. Previous workers using urine data after the administration of a solution of PPA suggested that the absorption of the drug could be described as biphasic, consisting of a slow phase followed by a much faster phase (Wilkinson and Beckett, 1968a). In the present study the initial absorption phase, which was a slow one, was followed by an extremely rapid rate of absorption (Table 2).

On the basis of their higher AIC values, the 1BCM and 2BCM with continuous first order absorption and the 1BCM with zero order absorption were disregarded. Although models A3 and

B3, both with 3 absorption rate constants, displayed the lowest AIC values, application of the F ratio test indicated no statistically significant difference between these models (A3 and B3) and those containing two absorption rate constants (A2 and B2). Both the 1BCM and 2BCM with two absorption rate constants were found to be equally appropriate, since no significant statistical difference was apparent between either of these models at the 99% significance level, as exemplified by the results of the F ratio test.

The semilog plots of serum concentration vs time after completion of absorption appeared to consist of two components, which would suggest the existence of a distribution phase in a 2BCM (Fig. 6). From observation of the individual sets of raw data and comparing them with the predicted fits, the disposition and elimination phases of the serum concentration-time curve were, in most cases, more accurately described using the 2BCM which accounts for loss of drug from the central compartment by two processes, elimination from the central compartment and transfer from the central into the peripheral compartment. However, intravenous data are necessary for the final elucidation of the disposition characteristics of a drug, and as only extravascular data were available in this study, the disposition of PPA into a 1BCM or 2BCM can only be postulated.

In summary, it has been shown that PPA exhibits rather unusual absorption characteristics and the drug's pharmacokinetic profile is well described using a discontinuous absorption model.

Acknowledgements

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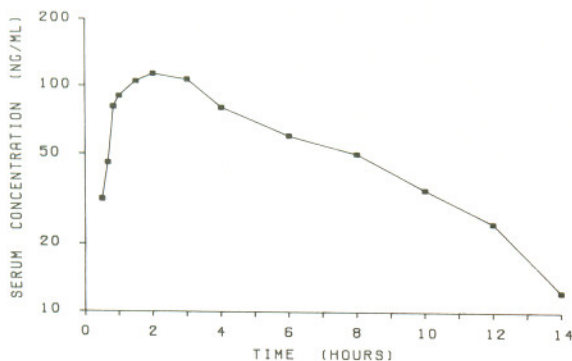
Fig. 6. Typical semilogarithmic plot of serum concentration vs time after oral administration of a 50 mg aqueous solution of the drug (Subject 2).

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