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THE PHARMACOKINETICS OF EPHEDRINE AFTER ORAL DOSAGE IN ASTHMATICS RECEIVING ACUTE AND CHRONIC TREATMENT

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1 Ephedrine plasma levels have been measured in ten asthmatic patients given a single dose of ephedrine hydrochloride (22 mg) alone and in combination with theophylline and a barbiturate.

2 Pharmacokinetic assessment of the data indicated no significant intra-subject changes in kinetic parameters before or after chronic treatment with ephedrine HCl (11 mg three times a day) alone or in combination.

3 Tolerance to these therapeutic doses, if it occurs, is therefore not disposition-related but rather related to pharmacodynamic changes.

Introduction

Ephedrine (2-methylamino-1-phenyl-1-propanol) is a naturally occurring alkaloid still extensively used for the treatment of bronchial asthma and upper respiratory tract disorders.

Herxheimer (1946) showed that patient sensitivity to this drug varied significantly and that a proportion of patients developed tolerance to the bronchodilator effects on repeated dosing.

The pharmacokinetics of ephedrine in man have been deduced from urinary measurement made in normal subjects under controlled conditions (Wilkinson & Beckett, 1968a; Welling, Lee, Patel, Walker & Wagner, 1971). A specific assay has been developed (Pickup & Paterson, 1974) in order to monitor plasma levels and study the pharmacokinetics of ephedrine following oral dosing with ephedrine in asthmatic patients. Studies have been performed in patients treated both acutely and chronically in order to investigate whether patient sensitivity and the development of tolerance could be related to specific changes in the disposition of ephedrine in the body.

Ephedrine is commonly given in a compound tablet such as Franol (Winthrop) which contains theophylline (120 mg), phenobarbitone (8 mg) and ephedrine hydrochloride (11 mg) for the treatment of asthma. Kinetic studies were carried out using one such combination (Tablet 4332, (ephedrine hydrochloride (10 mg), theophylline (125 mg) and phenobarbitone (7.5 mg)), Boots Company Limited) and using ephedrine alone in doses equivalent to that normally found in a compound tablet to investigate whether ephedrine disposition is affected by co-administration of these other drugs.

Methods

Subjects

Ten hospital outpatients, ranging in age from 25-51 years and receiving bronchodilator therapy (normally salbutamol) until the day preceding the investigation, volunteered for the studies. The one patient receiving ephedrine medication was asked to stop this 2 weeks prior to the investigation. All subjects were asked to minimize food and fluid intake on the morning of each study (e.g. fruit juice and a slice of toast), and at least 4 h elapsed after drug administration before lunch was taken.

Materials

(a) An oral dose of (−)-ephedrine hydrochloride (22 mg) was given in solution before (Study A1) and after (Study A2) 2 weeks' treatment with ephedrine hydrochloride (11 mg three times a day), and

(b) Two tablets 4332 were given before (Study B3) and after (Study B4) 2 weeks' treatment with one tablet three times a day.

A period of at least 2 weeks was allowed between (a) and (b) during which no ephedrine medication was prescribed.

The studies were carried out on each of ten patients; one patient (J.H.) withdrew, however, after Study A.

Plasma and urine collections

Ephedrine plasma levels were monitored in all studies; blood samples were drawn into lithium heparin tubes at approximately the following times for each study: 0 (i.e. the blank determination), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 hours.

Sufficient blood was taken to allow separation of the plasma into 2 x 3 ml portions. For Studies A1 and B3, 36 h urine samples were collected.

Analysis of plasma and urine ephedrine

Plasma samples were assayed by gas chromatography following ether extraction (Pickup & Paterson, 1974). Urine samples were assayed using a similar method modified to allow for the higher ephedrine concentrations obtained in urine. No attempt was made to measure urine or plasma levels of norephedrine, the major metabolite in man.

Pharmacokinetic assessment of data

Drug body level data can, in most circumstances, be assigned to either a one- or two-compartment open model (Notari, 1971; Reigelman, Loo & Rowland, 1968; Welling *et al.*, 1971). Pharmacokinetic assessment of the current data was carried out as described in the appendix, using both graphical and computer techniques.

Statistical analysis of data

The significance of any interstudy differences in calculated pharmacokinetic parameters within individuals was examined using a two-tailed paired *t*-test; the Student's *t*-distribution was used to test the null hypothesis that the average difference between individual pairs of results was zero. Linear least squares regression analyses (Hewlett-Packard programmable calculator 9810A) were performed to establish the significance of any correlation between calculated pharmacokinetic parameters.

Results

A typical plasma profile, measured as ng base/ml plasma at time t h, following dosage with two compound tablets is shown (Figure 1).

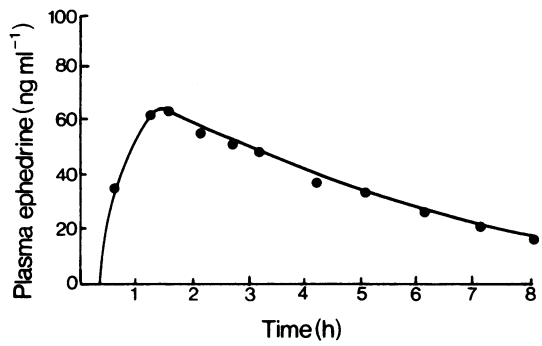

Figure 1 Ephedrine plasma levels following oral administration of two tablets 4332. Data from patient H.M., Study B3.

Data assessment

Pharmacokinetic parameters, calculated as described in the appendix, are presented in Tables 1-4.

(i) Peak plasma levels (C_m):–
Computer estimated peak plasma levels ranged from 52.7-138.8 (mean 79.4 ng ml^{-1}) following ephedrine dosage (Study A1). The times at which the peak occurred [t (C_m)] was an average 1.81 h after drug administration. In Study A2, peak plasma levels ranged from 66-118.6 (mean 87.4 ng ml^{-1}) occurring 1.86 h after administration. Similarly, for the compound tablet studies, a range of 44.7-111.1 (mean 73.9 ng ml^{-1}) was recorded after 1.69 h for Study B3, and a range of 65.7-107.3 (mean 77.2 ng ml^{-1}) after 1.47 h for Study B4.

(ii) Biological availability (f):–
The availability of ephedrine from the tablet form, assuming each tablet contains ephedrine HCl (11 mg), was calculated as 0.88.

(iii) Plasma half-life ($T_{\frac{1}{2}}$):–
These ranged from 4.48-11.48 (mean 6.75 h) for Study A1 (Table 1); 3.09-9.9 (mean 6.69 h) for Study A2 (Table 2); 3.54-10.45 (mean 5.74 h) for Study B3 (Table 3) and 3.29-8.56 (mean 5.22 h) for Study B4 (Table 4).

(iv) Plasma clearance ($\dot{V}_{pl}$):–
The mean clearance calculated in turn for each of the studies A1, A2, B3 and B4 was 23.3, 25.4, 28.7 and 30 litre h^{-1} respectively.

Table 1 Pharmacokinetic parameters for the acute ephedrine study—Study A1

Patient	Sex and weight (kg)	Dose given ≡ mg of ephedrine HCl	K_{abs}[1] (h^{-1})	t_o[2] (h)	C_m*[3] (ng ml^{-1})	$t(C_m)$*[4] (h)	β[5] (h^{-1})	$T_{\frac{1}{2}}$[6] (h)	A[7] (hng ml^{-1})	$\dot{V}_{pl}$[8] (litres h^{-1})	V_d[9] litres	36 h urine pH	36 h urine recovery (mg base)
L.H.	M,60	22	2.33	0.35	80.3	1.34	0.121	5.71	714.9	25.2	208.3	5.2	§
H.M.	F,69	22	1.02	0.00	80.7	1.01	0.138	5.01	626.4	28.8	208.7	5.3	14.6
J.B.	F,54	22	3.57	0.00	138.8	0.71	0.155	4.48	951.8	18.9	121.9	6.4	14.2
T.S.	M,67	22.11	2.97	0.00	75.7	1.39	0.115	6.01	711.9	25.5	221.7	5.9	14.7
R.L.	M,70	22	†	†	74.3	2.50	0.060	11.48	1327.7	13.6	226.7	§	§
P.W.	F,58	22	0.96	0.62	80.2	2.07	0.118	5.88	734.3	24.6	208.5	6.2	14.6
D.E.	M,75	22	4.28	0.32	79.1	1.36	0.078	8.91	1055.7	17.1	219.2	§	§
J.H.	M,79	20	†	†	52.7	3.58	0.081	8.60	780.2	21.0	259.3	5.8	§
D.S.	M,70	22	0.90	0.15	65.3	2.91	0.115	6.04	673.0	26.8	233.0	5.6	§
U.B.	M,75	22	2.73	0.00	67.0	1.23	0.128	5.41	567.0	31.8	248.4	5.8	16.7
Mean			2.35	0.18	79.4	1.81	0.111	6.75	814.3	23.3	215.6	5.8	15.0

† Insufficient data points for accurate determination
§ Not determined
* Computer estimated

1 Absorption rate constant
2 Lag time
3 Peak plasma level
4 Time of peak plasma level
5 Elimination rate constant
6 Plasma half-life
7 Area under plasma level curve
8 Plasma clearance
9 Apparent volume of distribution
10 Initial plasma level

Table 2 Pharmacokinetic parameters for the ephedrine study after chronic treatment — Study A2. The key to the numbers in the table headings is shown in Table 1

Patient	*Dose given ≡ mg of ephedrine HCl*	K_{abs}[1] *(h^{-1})*	C_{init}[10] *(ng ml^{-1})*	C_m*[3] *(ng ml^{-1})*	$t(C_m)$*[4] *(h)*	β[5] *(h^{-1})*	$T_{½}$[6] *(h)*	A[7] *(hng ml^{-1})*	$\dot{V}_{pl}$[8] *(litres h^{-1})*	V_d[9] *(litres)*	*36 h urine pH*
L.H.	22	1.70	0.0	73.4	0.88	0.127	5.46	524.5	34.4	270.9	5.4
H.M.	22	3.60	37.2	115.2	1.27	0.224	3.09	526.7	34.2	152.7	5.0
J.B.	22	1.40	29.1	118.6	1.83	0.095	7.30	1077.2	16.7	175.8	6.0
T.S.	22	1.77	14.9	88.4	2.33	0.107	6.48	803.6	22.4	209.3	5.6
R.L.	11	1.85	12.5	44.0	1.92	0.076	9.12	637.1	14.2	186.8	§
P.W.	22	1.08	16.1	68.0	2.27	0.070	9.90	805.7	22.4	320.0	6.1
D.E.	11	**	18.0	54.2	1.22	0.122	5.68	292.5	30.8	252.5	§
J.H.	22	0.62	17.0	85.8	3.33	0.083	8.35	937.9	19.2	231.3	5.8
D.S.	22	1.01	10.6	66.0	1.94	0.128	5.42	622.0	29.0	226.6	§
U.B.	22	0.92	6.8	83.8	1.61	0.113	6.13	581.7	31.0	274.3	6.1
Mean		1.55	16.2	87.4†	1.86	0.115	6.69	734.9†	25.4	230.0	5.7

* Computer estimated
** Insufficient data points for accurate determination
† R.L. and D.E. data omitted
§ Not determined

Table 3 Pharmacokinetic parameters for the acute compound tablet study—Study B3. The key to the numbers in the table heading is shown in Table 1

Patient	K_{abs}[1] (h^{-1})	t_o[2] (h)	C_m*[3] (ng ml^{-1})	$t(C_m)$*[4] (h)	β[5] (h^{-1})	$T_{½}$[6] (h)	A[7] (hng ml^{-1})	$\dot{V}_{pl}$[8] (litres h^{-1})	V_d[9] (litres)	*36 h urine pH*	*36 h urine recovery mg base*
L.H.	1.43*	0.00*	84.5	1.12	0.106*	6.54[a]	681.3	23.3	219.8[b]	5.3	§
H.M.	2.70	0.35	62.1	1.30	0.192	3.61	398.4	39.8	207.3	5.6	10.9
J.B.	4.17	0.45	111.1	0.76	0.103	6.75	1161.5	13.7	133.0	6.5	12.6
T.S.	2.29*	0.00*	99.6	0.65	0.147*	4.72[a]	523.4*	30.3	206.1[b]	5.5	13.8
R.L.	0.92*	0.47*	83.4	1.48	0.196*	3.54[a]	371.9*	42.7	217.9[b]	§	§
P.W.	0.81	0.80	57.0	2.46	0.144	4.81	529.7	30.0	208.3	6.6	14.5
D.E.	†	†	72.9	2.28	0.066	10.45	1075.9	14.7	222.7	§	§
D.S.	0.63	0.27	49.8	1.91	0.153	4.53	473.6	33.5	219.0	§	10.4
U.B.	0.90	0.70	44.7	3.26	0.104	6.67	527.2	30.1	289.4	6.8	10.0
Mean	1.73	0.38	73.9	1.69	0.135	5.74	638.1	28.7	213.7	6.1	12.0

† Insufficient data points for accurate determination
§ Not determined
* Computer estimated
[a] Equivalent to $T_{½}(\beta)$
[b] Equivalent to $V_d(\beta)$

Table 4 Pharmacokinetic parameters for the compound tablet study after chronic treatment—Study B4. The key to the numbers in the table headings is shown in Table 1.

Patient	K_{abs}[1] (h^{-1})	C_{init}[10] (ng ml^{-1})	C_m*[3] (ng ml^{-1})	$t(C_m)$*[4] (h)	β[5] (h^{-1})	T½[6] (h)	A[7] (hng ml^{-1})	$\dot{V}_{pl}$[8] (litres h^{-1})	V_d[9] (litres)	36 h urine pH
L.H.	†	17.0	75.0	0.65	0.108	6.42	510.6	31.1	288.0	5.5
H.M.	0.85	24.5	78.3	2.70	0.200	3.47	408.1	38.9	194.5	5.7
J.B.	0.84	34.1	107.3	1.77	0.117	5.92	894.0	17.8	152.1	5.9
T.S.	1.49	0.0	71.3	0.92	0.165	4.20	451.6	35.1	212.7	6.0
R.L.**	1.41	11.1	43.9	0.67	0.211	3.29	387.5	20.5	97.2	§
P.W.	0.74	10.2	68.7	2.43	0.144	4.81	366.6	43.3	300.7	5.5
D.E.**	†	70.5	118.0	1.11	0.081	8.56[a]	334.1	23.7	171.7[b]	§
D.S.	1.82	14.8	74.1	1.35	0.100	6.93	671.9	23.6	236.0	5.6
U.B.	0.93	0.0	65.7	1.66	0.204	3.40	437.5	36.3	177.9	5.9
Mean	1.15	20.2	77.2††	1.47	0.148	5.22	534.3††	30.0	203.4	5.7

† Insufficient data points for accurate determination
§ Not determined
* Computer estimated
** Received 1 tab only
†† R.L. and D.E. data omitted
[a] Equivalent to T½ (β phase)
[b] Equivalent to V_d (β)

(v) Apparent volume of distribution (V_d):–
The mean volume of distribution for each of the studies was found to be 215.6, 230, 213.7 and 203.4 litres respectively.

(vi) Plasma levels during the 2 weeks' chronic treatment:–
The approximate maximum and minimum plasma levels obtained for each patient during chronic therapy (ephedrine hydrochloride (11 mg) or one tablet 4332 every 8 h) are presented in Table 5.

(vii) Fitting of data to one- or two-compartment models:–
The majority of the individual studies carried out gave data which could reasonably be fitted to a one-compartment model. Assessment of the data in these cases was best carried out using graphical means, i.e. linear regression analysis and feathering techniques. In patients L.H., T.S., R.L. (Study B3) and patient D.E. (Study B4) the data could best be fitted to a two-compartment model. In patient D.E. graphical assessment of the data was preferred. The relative merits of graphical and computer techniques in assessing the data are discussed in the Appendix.

(viii) Statistical analysis:-
Results of paired *t*-tests indicated no significant ($P > 0.05$) difference in half-life, plasma clearance, rate constant and time of peak plasma level comparing data from:–

(a) Acute and chronic ephedrine studies (Tables 1 and 2 respectively).
(b) Acute ephedrine and acute compound tablet studies (Tables 1 and 3).
(c) Acute and chronic compound tablet studies (Tables 3 and 4).

There was no significant correlation between the pH of 36 h urine and the corresponding half-life in each subject. A significant correlation between the volume of distribution and the half-life could only be demonstrated in two patients (D.S., $P < 0.05$; U.B., $P < 0.001$). A significant correlation was obtained between body weight and volume of distribution in the acute studies A1 and B3 ($P < 0.01$ and < 0.05 respectively), and between body weight and the peak plasma level, C_m, in Study A1 only ($P < 0.05$).

Table 5 Estimated maximum (P_{max}) and minimum (P_{min}) ephedrine plasma levels during chronic treatment with ephedrine hydrochloride (11 mg three times a day) or tablets 4332 (1 three times a day). The figures represent plasma concentrations in ng base/ml calculated assuming one-compartment kinetics

	Ephedrine		*Tablets 4332*	
Patient	P_{max}[1]	P_{min}[2]	P_{max}[1]	P_{min}[2]
L.H.	52	19	48	20
H.M.	71	12	51	10
J.B.	96	45	86	34
T.S.	75	32	51	14
R.L.	106	58	100	18
P.W.	66	38	39	12
D.E.	57	21	97	51
J.H.	80	41	–	–
D.S.	62	22	61	27
U.B.	55	22	55	11
Mean	72	31	65	22

[1]Calculated using Equation 10
[2]Calculated using Equation 11

Discussion

Results indicate an availability from tablet of 0.88 based on the assumption that each compound tablet contains ephedrine hydrochloride (11 mg). In view of the rapid disintegration of the compound tablets (Nix, personal communication) i.e. 2-5 min (limit 15 min) by the BP method, and the high solubility of the drug, the availability seemed low and an alternative explanation was considered, i.e. that the tablets contained less ephedrine. This supposition was confirmed; tablet 4332 containing ephedrine hydrochloride (10 mg), anhydrous theophylline (125 mg) and phenobarbitone (7.5 mg) (Nix, personal communication). The dose of ephedrine administered in the tablet studies is thus only 90.9% of that given in the solution studies and this figure would explain the apparently lower availability from tablets (0.88) calculated on the assumption of equivalent doses. The comparable figures indicate a probable 100% absorption from tablet form.

The smaller ephedrine dose from the tablets was reflected also in the 36 h urine recoveries. Comparing the recovery (mg) in patients H.M., J.B., T.S., P.W. and U.B. after tablet dosage (Table 3) with the corresponding recovery after ephedrine dosage (Table 1) a mean ratio of 0.83 was obtained.

Ideally, each study should be continued for at least 3 times the calculated half-life of the drug. The dangers in assessing half-life over a short period of study have been discussed by Wagner (1963). The present studies were discontinued after 8 h since much longer times would have

reached the lower limit of accurate plasma ephedrine assay (Pickup & Paterson, 1974) and caused inconvenience to the patient. In two patient studies, plasma levels were cetermined after approximately 24 and 26 h and although accuracy could not be guaranteed at low plasma levels, these data points nevertheless fell on the exponential curve fitting points obtained up to 8 hours. Thus the terminal phase observed up to 8 h in each study appeared to represent the true elimination phase. This statement can be further justified in view of the comparable half-lives obtained for these studies (mean $T_{\frac{1}{2}}$ = 6.1 h) and the studies of Welling *et al.* (1971), where urinary estimations were carried out up to 36 h (mean $T_{\frac{1}{2}}$ = 5.65 or 5.99 h, depending on the method of assessment).

In agreement with the urine data of Wilkinson & Beckett (1968a & b), the majority of the concentration time profiles fitted fairly closely the one-compartment model, i.e. no evidence of a distribution phase. Four profiles were better fitted to the two-compartment model: a similar model was proposed by Welling *et al.* (1971) to fit ephedrine urine data. It seems probable that the tissue distribution of ephedrine is so rapid that in many studies it is not discernible, particularly where ingestion of food has been allowed (our studies and those of Wilkinson & Beckett, 1968a & b) and the distribution phase is consequently obscured by an extended absorption period. The tissue distribution of ephedrine is reflected in the calculated volumes of distribution (mean = 26 litres). This figure greatly exceeds total body water volume and is comparable with that found for similar basic drugs (Vree & van Rossum, 1970). The close fit of the regression line to the data points of the elimination phase [mean correlation coefficient (± s.e. mean) = 0.964 (± 0.0066)] indicates that small fluctuations in urine pH during a study have no significant effect on the plasma profile. This is in agreement with the results of Welling *et al.* (1971) who demonstrated no relationship between ephedrine excretion rates and fluctuating urinary pH in subjects with uncontrolled urine pH. Whilst small changes in pH may have no significant effect, it is certain that larger changes in urine pH can make appreciable differences to the overall ephedrine elimination rate (Wilkinson & Beckett, 1968b).

Figures presented for the lag time and absorption rate constant (Tables 1-4) are rough estimates only (see Appendix). However, the conclusion that the lag time, absorption rate constant and time of peak concentration are not significantly different whether the ephedrine is in solution or in tablet form is compatible with the reported rapid tablet disintegration and high drug solubility (see above), i.e. the dissolution process appears not to be rate limiting.

The lack of any significant intra-subject difference in calculated pharmacokinetic parameters before or after chronic treatment whether the ephedrine was given alone or in combination with theophylline and phenobarbitone implies that tolerance to the bronchodilator doses used in the present study, if it occurs, is not related to changes in ephedrine disposition in the body but is more probably due to pharmacodynamic changes.

Seven of the patients in the compound tablet study, B4, had half-lives which were shorter than in Study B3 (Tables 3 and 4). The mean difference, however, was not statistically significant. In many cases, the faster elimination after chronic treatment with tablet 4332 could be attributed to a greater plasma clearance rather than a decrease in volume of distribution. No comparable decrease was evident in comparing $T_{\frac{1}{2}}$ values calculated for the studies with ephedrine alone (A1 and A2, Tables 1 and 2). It may be deduced therefore that multiple dosing with a preparation containing theophylline or more probably phenobarbitone could influence ephedrine clearance, for example through enzyme induction, and this might become significant if the tablet dosing during chronic treatment were increased above that used in the present study.

Since concurrent drugs used between the studies were limited to small doses of bronchodilator aerosol drugs with subsequent minimal plasma levels, the possibility of drug interaction producing changes in pharmacokinetic parameters is unlikely. Despite the similarity in diet prior to each study, the large inter-subject variations recorded in the pharmacokinetic parameters and with few exceptions their independence of body weight, emphasize the difficulty in formulating standard dosage regimes. In addition there is a large inter-subject variation in the plasma level necessary to cause adequate bronchodilatation (May, Pickup & Paterson, 1975). Estimates of the maximum and minimum plasma levels during chronic treatment (Table 5) indicate a minimum range of 10-58 and a maximum range of 39-106 ng ml^{-1}. The figures, although approximate due to the nature of the equation used and the variability of dosage intervals in practice, are comparable with levels obtained after single dosing of 22 mg or two tablets 4332, suggesting that no appreciable build-up of drug in the patient occurred during chronic treatment with ephedrine hydrochloride (11 mg three times a day) or with the tablets (1 three times a day). The likelihood of side effects on this regime is thus no greater than that after acute dosing.

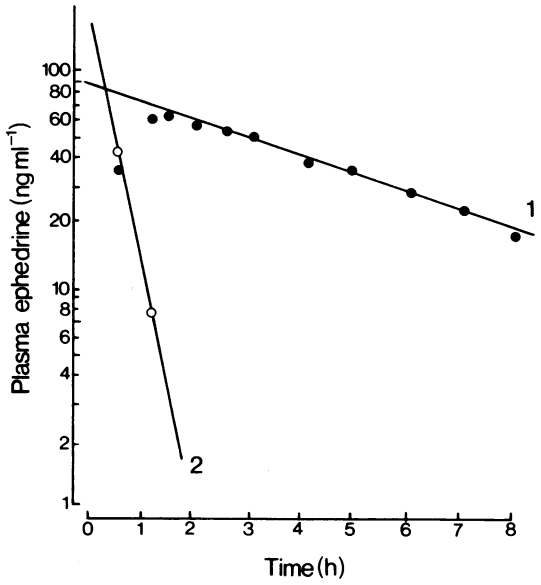

Figure 2 Semi-logarithmic plot to demonstrate the regression lines (1 and 2) constructed to fit respectively (i) the original data points (•) of the elimination phase and (ii) feathered points (○) obtained by subtracting the measured plasma concentration at a given time from the corresponding concentration on the regression line 1. Data from patient H.M., Study B3 fitted to a one-compartment model.

Appendix

Calculation of pharmacokinetic parameters from the concentration-time profile

Two methods, one graphical and one using a computer, were used to assess each concentration-time profile.

(1) *Graphical method*

Linear least squares regression analysis (Hewlett-Packard Programmable Calculator) was used to obtain the line of closest fit to the logarithms of the experimentally obtained data points of the terminal exponential phase (e.g. Figure 2, line 1). If the maximum recorded concentration (peak plasma level) was not significantly above this regression line, e.g. Figure 2, the pharmacokinetic parameters were estimated according to one-compartment kinetics:–

One-compartment model:– The rate constant for elimination of drug from the entire body β (one-compartment model) was calculated from the gradient, B, of the regression line drawn through the data points of the elimination phase according to Equation 1:–

$$\beta = -B \times 2.303 \qquad \text{Equation 1}$$

The plasma half-life of ephedrine, $T_{\frac{1}{2}}$, was calculated as:–

$$T_{\frac{1}{2}} = 0.6932/\beta \qquad \text{Equation 2}$$

The plasma clearance, $\dot{V}_{pl}$, of ephedrine was calculated from the dose, D, and its availability, f, according to Equation 3:–

$$\dot{V}_{pl} = f.D/A \qquad \text{Equation 3}$$

where A represents the area under the concentration, C, versus time, t, profile from zero to infinite time (Wagner, Northam, Alway & Carpenter, 1965) calculated as the sum of (i) the area obtained by cutting out and weighing the profile ($t = 0 \rightarrow 8$ h) drawn on paper of uniform thickness, subsequently converting to the units of h ng ml^{-1}, and (ii) the area calculated as C_8/β which represents the area from $t = 8 \rightarrow \infty$. C_8 is the ephedrine plasma concentration at $t = 8$ h as predicted by the regression line.

The volume of distribution, V_d, was calculated using Equation 4:–

$$V_d = \dot{V}_{pl}/\beta \qquad \text{Equation 4}$$

The absorption rate constant, k_{abs}, was obtained from the gradient, G, of the regression line drawn through the feathered points (e.g. Figure 2, line 2) according to Equation 5:–

$$k_{abs} = -G/2.303 \qquad \text{Equation 5}$$

In the acute studies, A1 and B3, the lag time, t_o, was taken as the time at which the regression lines (e.g. Figure 2, lines 1 and 2) intersect.

It should be noted that estimations of k_{abs} and t_o are subject to error due to the technique of 'feathering' itself and the lack of data points in the absorptive phase of each profile. Estimations were, however, carried out where possible for completeness.

Two-compartment model:– In those concentration-time profiles where the peak plasma level lay significantly above the regression line drawn through the terminal data points, i.e. where a distribution phase was evident, the half-life, volume of distribution and plasma clearance were estimated according to two-compartment theory (Notari, 1971).

Equations 1 and 4 were modified to read Equations 6 and 7 respectively:-

$$\beta = -B^1 \times 2.303 \qquad \text{Equation 6}$$

where B^1 is the gradient of the regression line through the data points of the terminal (β) phase only.

$$V_d(\beta) = \dot{V}_{pl}/\beta \qquad \text{Equation 7}$$

where $V_d(\beta)$ is an 'apparent' volume of distribution at pseudo-distribution equilibrium relating the total amount of drug in the body to the drug concentration in plasma at any time during the 'β' phase (Gibaldi, Nagashima & Levy, 1969).

Equations 2 and 3 were used unchanged.

Estimation of k_{abs} and t_o by graphical means in profiles showing two-compartment kinetics (Alexanderson, 1972) was not attempted due to the sparsity of data points in the absorptive phase.

(2) *Computer method:–*

The digital computer is the method of choice for the assessment of kinetic parameters. The experimental data points for each of the profiles studied were fed in turn into a digital computer (Control Data Corporation) programmed to assess the data in terms of a one-compartment and then a two-compartment model.

The computer was programmed first to make a direct prediction of the peak plasma level, C_m, and the corresponding time, $t(C_m)$, from the data points fed in, and then to assess the last three data points of each profile in order to calculate β. The computer was preset to 'look at' the last three points only since this was the maximum number of points certain to be on the true elimination phase of *all* the profiles studied. Computer assessment of β using earlier points would, in two of the studies, have been erroneous due to the absorptive and distributive processes being incomplete. The area under the concentration-time profile from zero to infinite time, A, was computer-estimated from the data points fed in up to 8 h and the calculated exponential decay from $t = 8 \rightarrow \infty$.

The computer initially assessed all data in terms of a one-compartment model making, as well as the above mentioned estimations, additional predictions of the absorptive rate constant, k_{abs}, and lag time, t_o. In those profiles where the *peak* plasma level data were significantly above the computer estimated regression line through the last three data points, one-compartment kinetics were rejected in favour of two-compartment; the computer subsequently estimating k_{abs}, t_o, k_{12}, k_{21} and k_{el} using two-compartmental theory. The rate constants k_{12} and k_{21} describe passage into and out of the 'tissue' compartment (distribution phase) and k_{el} is the rate constant for elimination of drug from the central compartment.

Following computer assessment of each profile, individual assessments of the half-life, plasma clearance and volume of distribution were made as described under *Graphical methods* using equations, 2, 3 and either 4 (one-compartment) or 7 (two-compartment model).

Relative merits of computer and graphically estimated parameters

The reliability of the computer estimates of A, k_{abs}, t_o, k_{12}, k_{21}, and k_{el} is dependent on the accuracy of the initial regression of only three experimentally obtained data points. It was therefore not surprising to find that computer predicted concentration-time profiles based on the computer derived parameters did not in many cases fit the original experimentally obtained profiles due to error primarily in assessing β. In the majority of studies, a closer fit was obtained using graphically derived parameters (see **Results**, Section vii). This could be explained in terms of the fact that the number of data points used to obtain β by graphical means (restricted to three by computer) could be varied with each profile such that the maximum number possible for each profile was considered. Use of earlier data points in calculating β was justified in terms of the closeness of fit of the regression line to the log concentration data during the elimination phase of each study .... mean r ($\pm$ s.e. mean) = 0.964 ($\pm$ 0.0066). The mean number of points used to calculate β graphically was 7.

The kinetic parameters listed in Tables 1-4 are therefore those which gave the closest fit to the experimental data. Where computer assessments gave the closest fit calculated figures for β, A, k_{abs} and t_o are denoted by an asterisk (Tables 1-4).

Area under plasma concentration-time profiles following chronic treatment

At the start (t = 0 h) of those studies following chronic treatment, the plasma ephedrine concentration was frequently above zero (concentration C_{init} .... see Tables 2 and 4), due to residual ephedrine from the last dose of the chronic treatment period the previous day. This resulted in an increase in the area under the profile, greater by an amount given by:–

$$A_m = C_{init}/\beta \qquad \text{Equation 8}$$

where A_m is the contribution to the total area under the concentration-time curve resulting from an assumed mono-exponential elimination of the initial concentration, C_{init} .... elimination rate

constant β. In studies A2 and B4, therefore, the true area following a single oral dose of either ephedrine HCl (22 mg) or two compound tablets, recorded in Tables 2 and 4 respectively, was obtained by subtracting from the total area the appropriate calculated value of A_m.

Biological availability, f

The theoretical aspects of bio-availability have been discussed by Gibaldi, Boyes & Feldman (1971) and by Rowland (1972). For the purpose of subsequent calculations (Equations 3 and 10) the availability of ephedrine from solution (Studies A1 and A2) was assumed to be 1.0 . . . . a decision justified in view of the almost identical recovery of ephedrine obtained after per oral and intravenous administration of the hydrochloride in solution (Wilkinson & Beckett, 1968b).

The availability from tablet form (Studies B3 and B4) relative to that from solution was calculated from the relative areas under the mean plasma concentration versus time profiles, omitting data from patient J.H. such that profiles from equivalent sample numbers could be compared. The areas under these profiles (calculated graphically), the corresponding half-lives and the availability, calculated using Equation 9 are presented in Table 6. The availability from tablet form is given by:–

$$f = A_{tab}/A_{soln} \qquad \text{Equation 9}$$

where A_{tab} and A_{sohn} are the areas under the plasma concentration-time profiles ($t = 0 \rightarrow \infty$) after oral administration of equivalent doses of drug given in tablet form and solution respectively to the *same* group of subjects. The equation is valid only where the initial (t = 0 h) concentrations and elimination rate constants after solution and tablet dosage are comparable (see Table 6) and where the availability from solution is 100%. A mean of the two estimations of f (Table 6) was used in subsequent calculations for the tablet studies.

Calculation of approximate peak and through plasma leves during the two weeks' chronic treatment

Assuming one-compartment kinetics and a rapid absorption of drug, the *approximate* peak plasma level (P_{max}ng ml^{-1}) during chronic treatment can be estimated from Equation 10:–

$$P_{max} = f\, x_o/(1 - e^{-\beta\, t_i})\, V_d \qquad \text{Equation 10}$$

where x_o is the maintenance dose (ng *base*), f the availability, t_i the dosage interval in hours, and V_d the volume of distribution in ml.

The minimum plasma level (i.e. in the trough immediately preceding the next dose) is given by:–

$$P_{min} = P_{max}\, e^{-\beta\, t_i} \qquad \text{Equation 11}$$

Equations 10 and 11 are modifications of those given by Goldstein, Aronow & Kalman (1974).

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Table 6 Pharmacokinetic parameters estimated from the mean plasma level data of equivalent sample numbers and used to calculate the availability of ephedrine from tablet form (see Equation 9)

	Study			
	Acute		*Chronic*	
Parameter	A1	B3	A2	B4
Area under curve $t = 0 \rightarrow \infty$ (h ng ml^{-1})	751	655	781	692
$T_{½}$(h)	5.62	6.40	5.84	5.53
Availability from tablet (f)	0.87		0.89	

Mean f (used in Equations 3 and 7) = 0.88

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