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Comparative pharmacokinetics of theophylline and ethylenediamine following single and repeated doses of a sustained-release aminophylline preparation to volunteers

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Plasma concentrations of theophylline and ethylenediamine have been measured by HPLC after a single dose and also after a further four consecutive doses at 12 h intervals of a tablet containing 225 mg aminophylline in a sustained release matrix (Phyllocontin) had been taken by volunteers. A dissolution study of the product showed the release of theophylline to follow zero-order kinetics, to be independent of bath pH, and to be complete in 6·5 h, while the release of ethylenediamine depended upon the pH of the medium and was more extensive in acid solutions. After one tablet, the plasma theophylline concentrations reached a maximum of 4 μg ml^{-1} at 5 h and fell slightly at 7 h. Immediately before the fifth dose, the trough plasma value was 4·7 μg mol^{-1}, and this rose to 7·7 μg ml^{-1} 5 h after the dose. The areas under the plasma level-time curves (AUC) were significantly ($P < 0·001$) increased by the chronic regimen, and although the individual values were highly variable, the increase in AUC from the first to the fifth dose was significantly ($P < 0·001$) correlated within each subject. Ethylenediamine concentrations after a single dose reached a peak of 0·16 μg ml^{-1} at 1 h, and returned to baseline values in 5–7 h. After the fifth dose, the plasma levels and kinetics were no different from those obtained with the first dose indicating that ethylenediamine did not accumulate as a result of chronic administration of aminophylline in a form designed to give steady-state levels of theophylline.

There is a good relation between the therapeutic effect of theophylline and its concentration in the plasma. The usual range quoted as giving the desired effect is from 8–10 up to 15–20 μg ml^{-1} (Ogilvie 1978). Lower values are generally ineffective, while toxic effects ranging from nausea and vomiting to cardiac arrhythmias ensue when the plasma level is sustained above 20 μg ml^{-1} (Ogilvie 1978). Its pharmacokinetic characteristics are such that maintenance of plasma levels within the desired range is difficult. The mean plasma elimination half-life is 6–8 h, so that even if the drug is given every 6 h, the peak-to-trough variation in plasma will be substantial. There is also wide inter-individual variation in theophylline pharmacokinetics: in particular, the plasma elimination half-life varies about five-fold about the mean (see Ogilvie 1978: Caldwell et al 1981). The desirability of maintaining theophylline plasma levels within a narrow, well-defined range in the face of this pharmacokinetic variability has led to the development of sustained release formulations and these have almost supplanted conventional preparations for oral administration (see Weinberger & Hendeles 1983). Because of theophylline's poor solubility, it is combined with ethylenediamine as aminophylline, but unlike most excipients ethylenediamine is not biologically inert. It is thought to contribute to the respiratory and cardiovascular effects of aminophylline and is well-known to produce both immediate and delayed hypersensitivity reactions when applied topically or injected intravenously (cf. Cotgreave & Caldwell 1983a; Thompson et al 1984), although such allergic reactions are apparently much less frequent when aminophylline is taken by mouth.

We have previously established the pharmacokinetics of ethylenediamine following the administration of aminophylline as conventional tablets and by intravenous infusion (Cotgreave & Caldwell 1983b, c). The results showed that theophylline and ethylenediamine are dealt with separately by the body, ethylenediamine having much the shorter elimination half-life and smaller volume of distribution. In view of the widespread use of controlled-release preparations of aminophylline, it is relevant to examine the pharmacokinetics of ethylenediamine

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after single and multiple doses of such a preparation, especially in relation to the possible accumulation of ethylenediamine in the body. In this paper, we present the results of a study on a widely used controlled-release aminophylline formulation (Phyllocontin). A preliminary account of these data was presented at the 9th International Congress on Pharmacology, London, 1984 (Caldwell & Cotgreave 1984).

MATERIALS AND METHODS

Compounds

Tablets containing 225 mg aminophylline in a controlled release formulation, Phyllocontin batch no. 1021, were a gift from Napp Laboratories Ltd, Cambridge, UK. Other compounds were as described by Cotgreave & Caldwell (1983b, c).

Volunteer studies

Six healthy volunteers (5M, 1F), ages 20–28 years, 48–95 kg, who gave their informed consent, participated in the investigation which was approved by the Ethical Committee of St Mary's Hospital and Medical School. The subjects maintained their usual intake of methylxanthine-containing foods and beverages, and restricted their alcohol intake to the equivalent of two pints of beer per day during the study. No other drugs were taken for at least one week before and during the study.

After a light breakfast, each subject took a single tablet at 9.00 h with 50 ml of water. No solid food was taken for at least 3 h. Blood samples (5 ml) were taken by venepuncture immediately before and at 30, 60, 120, 180, 300 and 420 min after dosing, into tubes containing lithium heparin and the plasma was then separated by centrifugation (1000*g*, 10 min) and stored at −20 °C. Then at four 12 h intervals the subjects took 4 further tablets and blood samples (5 ml) were taken immediately before, and at 60, 120, 180, 300 and 420 min after the last dose, and plasma separated and stored as above.

The concentrations of theophylline and ethylenediamine in each plasma sample were determined by HPLC (Cotgreave & Caldwell 1983b, c).

Tablet dissolution studies

The dissolution of theophylline and ethylenediamine from the tablets was assessed as described in the British Pharmacopoeia (1980). The bath (1 litre volume), thermostatted at 37 °C, was filled with 0·6% HCl for the first hour, and then with 1·5% w/v $NaHCO_3$, changed at regular intervals up to 6·5 h. Concentrations of theophylline and ethylenediamine were assayed by HPLC.

RESULTS

Dissolution of theophylline and ethylenediamine from sustained release tablets

As seen from Fig. 1, the release of theophylline is slower, but more extensive, than that of ethylenediamine, and follows zero-order kinetics, independent of the pH of the bath solution. In contrast, ethylenediamine is released more rapidly into the acid solution, thereafter exhibiting an apparent first-order dissolution into the alkaline solutions. The cumulative recovery of theophylline is within 2% of the stated content, but that of ethylenediamine is some 25% less. Ethylenediamine was stable in the acid and alkaline bath solutions at 37 °C.

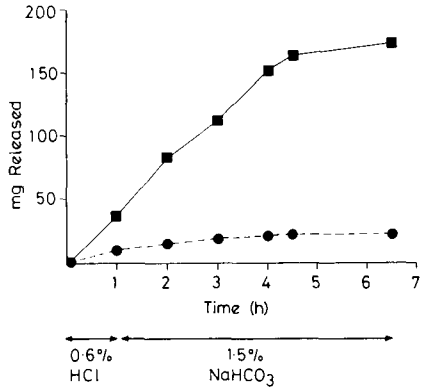

FIG. 1. Release of theophylline and ethylenediamine from sustained release tablets in-vitro. Tablets containing 225 mg aminophylline in a sustained release matrix were placed in a dissolution apparatus containing 0·6% HCl for the first hour and 1·5% $NaHCO_3$ thereafter as described in the text. Aliquots of the bath fluids were assayed for theophylline and ethylenediamine by HPLC at intervals for up to 6·5 h. Data points are the means of two estimations at each time: individual values varied by no more than 5% in all cases. Key: (■), theophylline; (●), ethylenediamine.

Plasma pharmacokinetics of theophylline and ethylenediamine following single and multiple doses of sustained release tablets to volunteers

Theophylline

Plasma levels of theophylline following the first and fifth dose of the tablets to volunteers are presented in Fig. 2. Following the initial dose, the plasma level of theophylline rose from the mean dietary baseline level of 0·9 μg ml^{-1} to a maximum of 4 μg ml^{-1} at 5 h, and fell slightly at 7 h. Immediately before the fifth dose, the trough plasma value was 4·7 μg ml^{-1}, which rose steadily to 7·7 μg ml^{-1} at 5 h. The areas under the 0–7 h plasma level-time curves following the first and fifth doses were calculated by the trapezoidal rule, and normalized to body weight, and

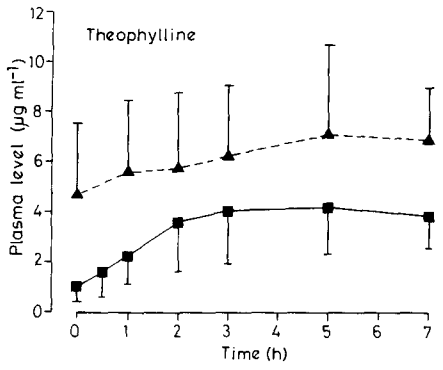

FIG. 2. Plasma concentrations of theophylline in six volunteers following the administration of single and five repeated doses of tablets containing 225 mg aminophylline in a sustained release matrix. Data are the mean ± s.d. at each time. The experiment is described in the text. Key: (■), first dose; (▲), fifth dose.

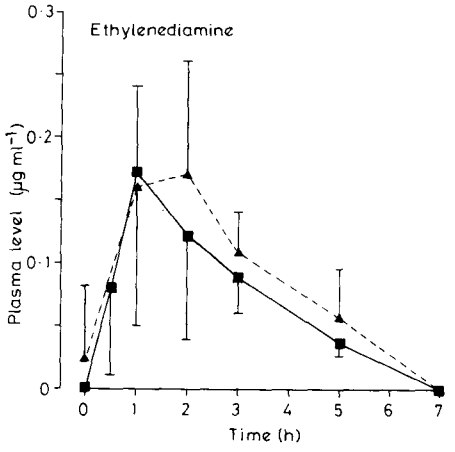

FIG. 3. Plasma concentrations of ethylenediamine in six volunteers following the administration of single and five repeated doses of tablets containing 225 mg aminophylline in a sustained release matrix. Data are the mean ± s.d. at each time. The experiment is described in the text. Key: (■), first dose; (▲), fifth dose.

are compared in Table 1. The first and fifth dose AUCs were compared by the paired two-tailed Student's *t*-test and there was a significant increase upon chronic administration. Although the individual AUC values were highly variable, Spearman rank correlation of the first and fifth dose AUCs shows them to be significantly correlated within each subject (Table 1).

Ethylenediamine

Plasma levels of ethylenediamine following the first and fifth doses of the tablets to volunteers are shown in Fig. 3. After the first dose, the peak plasma value was 0·16 μg ml^{-1}, achieved at 1 h, and this declined monoexponentially thereafter, falling below the lower limit of detection 5–7 h after dosing. Before the fifth dose, three of the subjects had trace (mean 0·03 μg ml^{-1}) amounts of ethylenediamine in their plasma; in the other three, values were never greater than 0·03 μg ml^{-1}. Following the fifth dose, the peak plasma value of 0·16 μg ml^{-1} was obtained at 2 h, again becoming undetectable 5–7 h after dosing. The ethylenediamine first and fifth dose AUCs were compared as for theophylline, and were not significantly different (Table 1). Again, the individual AUC values were highly variable between the subjects.

DISCUSSION

Data presented here show that ethylenediamine does not accumulate in the plasma of volunteers receiving

Table 1. Areas under the plasma concentration-time curves (AUC) for theophylline and ethylenediamine after the oral administration of single and five repeated doses of tablets containing 225 mg aminophylline in a sustained release matrix to six volunteers. Differences were tested for significance by the paired two-tailed Student's *t*-test, and associations between Dose 1 and Dose 5 data, where different, examined by the Spearman rank correlation.

			Theophylline				Ethylenediamine			
			AUC (μg h ml^{-1})		Normalized AUC (μg h ml^{-1} kg^{-1})		AUC (μg h ml^{-1})		Normalized AUC (μg h ml^{-1} kg^{-1})	
Subject	Sex	Wt (kg)	Dose 1	Dose 5	Dose 1	Dose 5	Dose 1	Dose 5	Dose 1	Dose 5
1	M	95	13·65	27·75	0·144	0·292	0·335	0·430	0·0035	0·0045
2	M	70	14·65	20·15	0·209	0·288	0·450	0·395	0·0064	0·0056
3	M	72	18·95	33·70	0·263	0·468	0·505	0·995	0·0070	0·0138
4	M	65	24·55	52·45	0·378	0·807	0·433	0·580	0·0067	0·0089
5	M	66	28·81	41·70	0·437	0·632	0·595	0·705	0·0090	0·0107
6	F	48	42·98	80·55	0·895	1·678	0·790	2·550	0·0165	0·0531
Mean			23·93	42·71	0·388	0·694	0·518	0·942	0·0082	0·0161
s.d.			10·03	19·76	0·247	0·476	0·146	0·746	0·0041	0·0168
P			<0·05		<0·05		n.s.		n.s.	
$R_{(s)}$			0·986		0·986		—		—	
ρ			<0·001		<0·001		—		—	

a controlled release aminophylline preparation, under a dosage regimen designed to give steady-state plasma concentrations of theophylline.

Dissolution studies showed that although the formulation was designed to provide a sustained release of theophylline under physiological conditions (Boroda et al 1973), a measure of sustained release of ethylenediamine also occurs. The release of theophylline from the matrix follows apparent zero-order kinetics, and is essentially independent of the pH of the bath fluid. However, the dissolution of ethylenediamine, a strong base, is much more extensive into the acid solution than into alkaline media. It seems likely that ethylenediamine is not completely released from the matrix, as the recovery was less than the stated content.

The plasma pharmacokinetics of theophylline we found are similar to literature values (Boroda et al 1973; Trembath & Boobis 1979). Thus, the plasma concentrations of theophylline approach steady-state in each of the subjects, with an observed peak-to-trough range of 2·2 $\mu g\ ml^{-1}$ during the fifth dosing period. This represents a fluctuation of 48%, which is in agreement with data obtained with this formulation by Trembath & Boobis (1979) and is broadly similar to results with other sustained-release preparations of theophylline and aminophylline (see Weinberger & Hendeles 1983 who also report that conventional formulations of theophylline give rise to much greater variability in peak-to-trough concentrations).

Comparison of the plasma pharmacokinetics of ethylenediamine observed here with those reported for conventional tablets of aminophylline B.P. (Cotgreave & Caldwell 1983c) show that although the peak plasma values achieved are similar measurable concentrations are sustained for longer (5–7 h, compared with 2–3 h) with the sustained release tablet which is in accord with the dissolution findings, while on repeated administration of the tablet the plasma pharmacokinetics of ethylenediamine were no different from the first dose. When these results are compared with data from conventional formulations (Cotgreave & Caldwell 1983c), after correction for differences in dose size, the peak plasma values of ethylenediamine in the two studies were similar, but their time courses were dependent upon the formulation used. Following a conventional aminophylline tablet, theophylline was absorbed more rapidly than ethylenediamine, but this situation was reversed with the controlled release formulation. This is consistent with the more rapid release of ethylenediamine from the tablet matrix into acid solution in-vitro, as might be expected to occur in the stomach. Following the administration of the sustained release product, both theophylline and ethylenediamine persist in the blood for longer than after the conventional tablet. But, although ethylenediamine persists for longer in plasma compared with conventional tablets, its metabolic clearance is sufficiently high (ca 580 $ml\ min^{-1}$; Cotgreave & Caldwell 1983c) to prevent its accumulation in the body during the administration of the recommended dose regimen of the controlled-release formulation. Therefore, since ethylenediamine is cleared from the body faster than theophylline, any effects it might exert will be transient compared with those of theophylline. In addition, the extensive first-pass metabolism of ethylenediamine and consequent low plasma levels found after oral administration (Cotgreave & Caldwell 1983b) render any role for ethylenediamine in the biological effect of aminophylline even less likely when aminophylline is given orally.

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