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COMPARATIVE PHARMACOKINETICS OF THEOPHYLLINE AND AMINOPHYLLINE IN MAN

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1 The pharmacokinetics of theophylline and aminophylline was compared after oral administration and intravenous infusion.

2 Theophylline (250 mg) and aminophylline (390 mg) were taken orally by eight healthy volunteers in a randomized cross-over study.

3 In another cross-over study theophylline and aminophylline were administered intravenously to six healthy volunteers at a dose corresponding to 5 mg/kg pure theophylline.

4 The protein binding of theophylline in serum collected during the intravenous study was studied by ultrafiltration. The serum concentration of theophylline was measured by high pressure liquid chromatography.

5 Almost identical concentration-time curves were found for theophylline and aminophylline in both of the studies. No significant difference was found in the pharmacokinetic parameters or protein binding with the two preparations.

Introduction

Theophylline is poorly soluble in water, but the solubility increases considerably after addition of ethylenediamine to form the complex salt aminophylline. For few drugs have the dosage schedules been more meticulously designed after detailed pharmacokinetic studies in healthy volunteers and in patients from different age groups and with various pathological conditions (Ogilvie, 1978). By far the majority of these studies have been carried out with aminophylline, but some oral experiments with pure theophylline have also been published (Sansom, Milne & Cooper, 1979; Talseth, Boye & Bredesen, 1979).

After single dose experiments with ^{14}C-labelled theophylline and aminophylline given intravenously to three healthy volunteers Caldwell, Monks & Smith (1978) claimed that there is a significant change in the metabolism of theophylline in the presence of ethylenediamine. However, in clinical practice no distinction is made between the two derivatives, the recommended dosage being identical with regard to the amount of active substance.

Some reports of allergic reactions toward ethylenediamine have appeared (White, Douglas & Main, 1978; Petrozzi & Shore, 1976). Because of this risk and the fact that pure theophylline is well absorbed from the gastrointestinal tract in spite of its low solubility (Hendeles, Weinberger & Bigley, 1977), it is quite understandable that theophylline has been chosen for most modern sustained release preparations for long term treatment of asthma. Parenteral formulations containing pure theophylline or other soluble salt or complexes may also become available in the future. It was therefore deemed of interest to see if ethylendiamine influences the overall pharmacokinetics and the binding of theophylline to serum proteins. The present report describes a series of cross-over experiments with theophylline and aminophylline given intravenously or orally to healthy volunteers.

Methods

Oral administration

Eight healthy male subjects volunteered for the study. Their ages were between 24 and 37 years (mean 32 years) and their body weights ranged from 67 to 104 kg (mean 80 kg). The volunteers had no history of renal, gastrointestinal or hepatic disease, and their renal function was normal as judged by the serum creatinine concentration. Haematological status and liver function tests were normal. The subjects were

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informed about the purpose of the study and possible risks before giving their consent to participate.

The drugs given were two 125 mg tablets of microcrystalline theophylline (Nuelin, 3M Riker) and two 195 mg tablets of aminophylline (Theodrox, 3M Riker). Accordingly, due to the tablet strength, the total dose of the latter product (308 mg pure theophylline) was 23% higher than with the former preparation. The *in vitro* dissolution characteristics of the drugs were determined in simulated gastric juice according to USP XIX using a rotating basket at a speed of 50 rev/min. The time needed for 50% and 90% dissolution of the aminophylline tablets was 25 and 60 min, respectively. The corresponding values for the theophylline tablets were 5 and 15 min.

The study was carried out according to a randomized cross-over design, and the interval between the two drugs was at least 1 week. The subjects were asked to refrain from ingestion of tea, coffee or chocolate 24 h before and during the experiments. The experiments commenced in the morning 0.5 h after the subjects' usual continental breakfast. A blood sample (blank) was taken from a catheter inserted into a forearm vein and the tablets were swallowed with 150 ml water. Blood samples were then collected at 30 min, 1, 2, 3, 4, 6, and 10 h while the subjects were performing light laboratory work. Serum was separated by centrifugation and stored at −20°C until analysed.

Intravenous administration

A second group of volunteers were selected according to the criteria applied in the first study. Their ages were between 24 and 38 years (mean 33 years) and their body weights ranged from 62 to 76 kg (mean 69 kg).

The following preparations were administered: (1) A sterile solution of theophylline (5 mg/ml) with the addition of NaCl, 8.42 g/l and 1 M NaOH solution to pH 7.35 (A/S Farmaceutisk Industri, Oslo). (2) Aminophylline 30 mg/ml injectable (NAF-laboratoriene, Oslo) was diluted with sterile saline to 5.9 mg/ml to match the theophylline concentration of (1). The theophylline concentration of the solutions was verified by high pressure liquid chromatography.

The study was carried out according to a randomized cross-over design, and the interval between the two experiments was at least 1 week. In the morning 1–2 h after the subjects usual continental breakfast (excluding xantine-containing beverages) a dose of either solution corresponding to 5 mg/kg pure theophylline was administered by linear infusion (Infusomat, Braun, Melsungen) into a forearm vein over a period of 20 min. Venous blood samples (2 ml) were taken before the experiments (blank), immediately after the infusion, and then after 5, 10, 20, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h. The subjects were lying down for 1 h after the start of the infusion and were carefully monitored with frequent blood pressure and pulse registrations.

Protein binding

The binding of theophylline was measured in serum obtained from the intravenous experiments with theophylline and aminophylline. A larger blood sample (10 ml) was collected 20 min and 3 h after the end of the infusion, and the serum was stored at −20°C until analysed.

The protein binding was studied by ultrafiltration according to Simons, Simons, Briggs & Lo (1979) with a few modifications. The membrane cones (Amicon CF-50A) were filled with 3 ml serum, flushed for 2 min with 5% CO_2 to prevent pH changes (Vallner, Speir, Kolbeck, Harrison & Brandsome, 1978), and the system was covered with Parafilm®. The cones were centrifuged three times for 5 min at 300 *g* to produce approximately 100 μl of ultrafiltrate each time. The concentrations of theophylline was measured in the original samples and in the two last ultrafiltrates. Some absorption of theophylline by the cones was observed after the first centrifugation, but there was no evidence of losses during the subsequent ultrafiltrations. The protein concentration was measured in the ultrafiltrates (Lowry, Rosebrough, Farr & Randall, 1951) and was between 5 and 10% of the level in serum.

Analysis and calculations

Serum theophylline was measured by the high pressure liquid chromatographic method of Orcutt, Kozak, Gillman & Cummings (1977) with minor modifications. The absorbance detector (Model 440, Waters Ass.) was fitted for continuous monitoring of the eluent at 280 nm, the mobile phase was acetonitrile/sodium acetate buffer (10 mmol/1, pH 4.0) 10/90 v/v, and serum proteins were precipitated with acetonitrile containing the internal standard, β-hydroxyethyltheophylline.

In the oral study the elimination constant (k_{el}) and the elimination half-life ($T_{½}$) were calculated by linear regression of the serum concentrations at 4 h, 6 h, and 10 h. The area under the concentration-time curve from zero time to 10 h ($AUC_{0-10\,h}$) was calculated by the trapezoidal rule and the area from the last observation ($C_{10\,h}$) to infinity ($AUC_{10\,h-\infty}$) was taken as $C_{10\,h}/k_{el}$. The maximal concentration (C_{max}) and the time to reach the peak (t_{max}) were read directly from the individual curves.

The pharmacokinetic parameters derived from the intravenous study were calculated by exponential regression according to a two-compartment open model using a desk computer (Hewlett-Packard, model HP-9825) and a program designed by Foster & Bourne

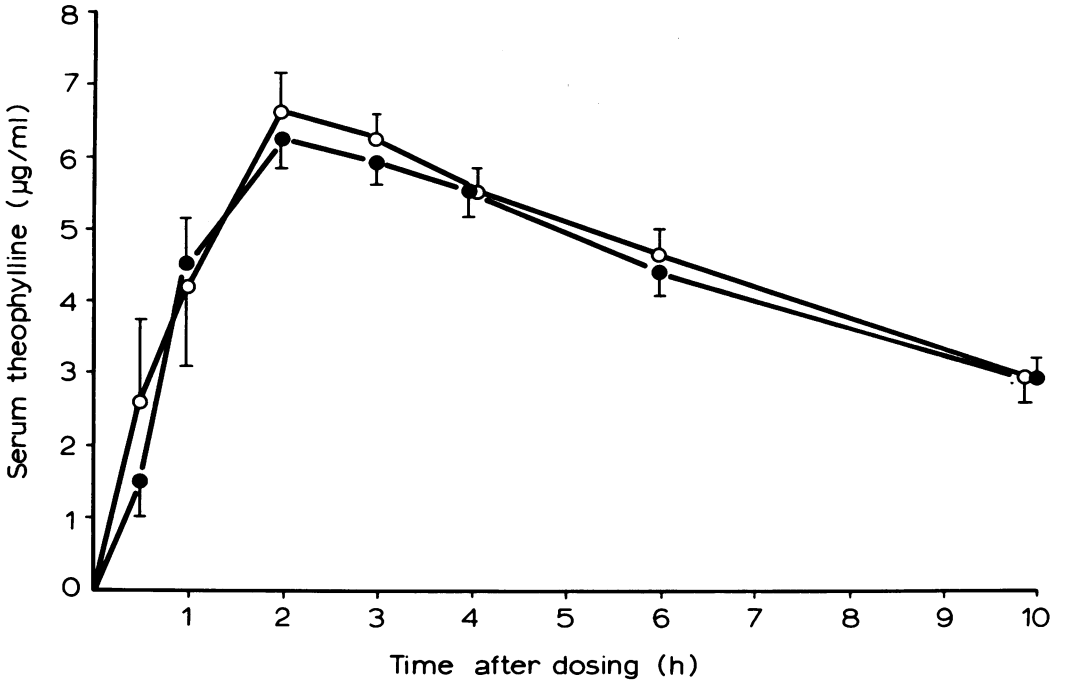

Figure 1 The serum concentrations (mean and s.e. mean) of theophylline in healthy volunteers (n=8) after oral administration of theophylline 250 mg (●) and of aminophylline 390 mg (○). The latter concentrations are corrected to 250 mg pure theophylline.

(1977). Completion of the administration was taken as zero time and no correction was made for the duration of the infusion.

The protein binding (b) was calculated using the formula: $b=D_t-D_f/D_t$, where D_f is the mean drug concentration of the last 2 ultrafiltrates and D_t the total drug concentration in serum.

Statistical analysis was performed using Wilcoxon's test for pair differences, and the limit of significance was set at $P \leq 0.05$.

Results

Oral study

The mean concentration-time curves of theophylline and aminophylline are presented in Figure 1. The curves were almost identical for the two preparations, both showing a reasonably rapid absorption phase with maximal serum concentrations after 2 h. The derived pharmacokinetic parameters shown in Table 1 were not significantly different with the two formulations.

Intravenous study

The mean concentration-time curves (Figure 2) were indistinguishable with theophylline and aminophylline. The derived pharmacokinetic parameters are presented in Table 2. There was a two-fold inter-individual variation in the elimination half-life with both preparations, whereas the volume of distribution in relation to body weight was fairly constant. Significant differences between the two preparations were not recognized for any of the parameters.

Table 1 Pharmacokinetic parameters in healthy male volunteers (n=8) after oral administration of theophylline (250 mg) and aminophylline (390 mg). C_{max} and AUC for aminophylline are corrected to 250 mg pure theophylline.

Pharmacokinetic parameters	*Theophylline*		*Aminophylline*	
	Mean	*Range*	*Mean*	*Range*
Maximal serum concentration, C_{max} (mg/l)	6.5	5.5–7.5	6.9	5.1–8.9
Time to maximal serum concentration, t_{max} (h)	2.1	1–3	1.9	0.5–3
Elimination half-life, $T_{½}$ (h)	7.0	3.2–12.4	6.9	3.9–13.0
Elimination constant, k_{el} (h^{-1})	0.112	0.056–0.214	0.114	0.053–0.177
Area under concentration curve 0–10 h, $AUC_{0-10\,h}$ (mg/h/l)	44.0	33.4–54.7	45.3	32.5–62.3
Area under concentration curve 0–∞, $AUC_{0-\infty}$ (mg/h/l)	76.2	38.5–122.8	75.7	41.3–117.3

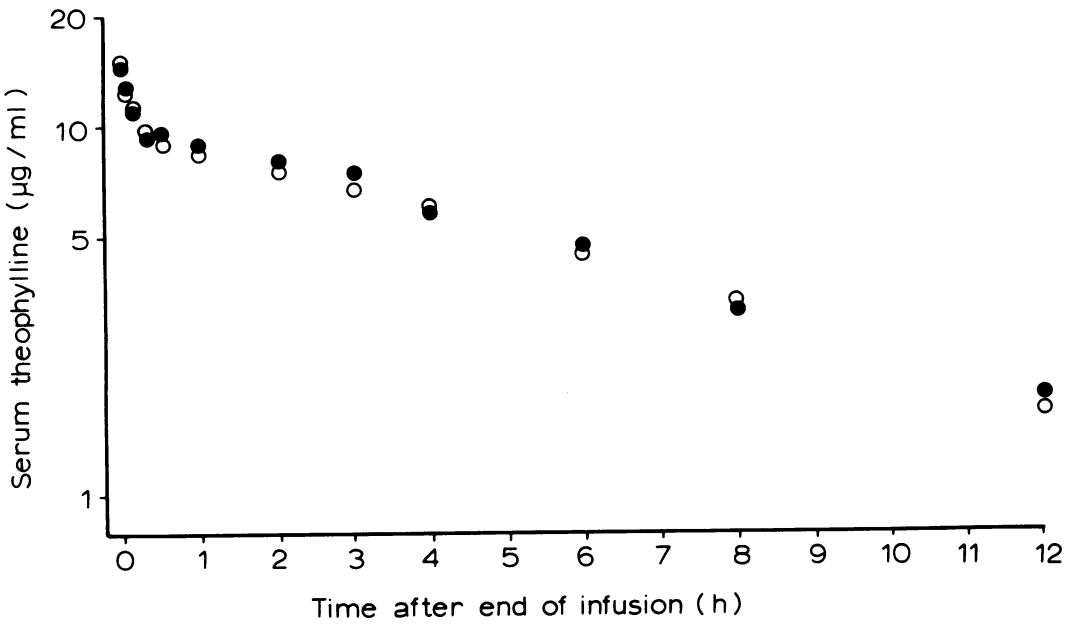

Figure 2 The mean serum concentrations of theophylline in healthy volunteers (n=6) after infusion of 5 mg/kg of theophylline (●) and an equivalent dose (5.9 mg/kg) of aminophylline (○).

Protein binding

The results of the protein binding experiments are summarized in Table 3. The binding was in the range of 48–70% for theophylline and 49–73% for aminophylline, and there was no significant difference between the two preparations.

Side effects

One subject complained of tremor of approximately 1 h duration beginning shortly after completion of the intravenous infusion of aminophylline. No other adverse effects were recorded.

Discussion

The finding of similar serum concentration-time profiles with microcrystalline theophylline and conventional aminophylline tablets is in accord with the recent report of Sansom *et al.* (1979). Since the *in vitro* dissolution times of the aminophylline formulation (Theodrox) were considerable longer than those observed with the pure theophylline tablets (Nuelin), it appears that dissolution is not a rate limiting factor for the absorption of these drugs *in vivo*.

Caldwell *et al.* (1978) studied the pattern of urinary metabolites and their rates of excretion in three healthy volunteers after intravenous administration of [^{14}C]-theophylline with and without ethylenediamine. The recovery of ^{14}C in the urine was higher and the excretion of label was more rapid for aminophylline than with theophylline. The rate constant of the elimination of the metabolite 1,3-dimethyl-uric acid was also increased for aminophylline.

We have not studied the production of metabolites, but the cross-over experiments with oral and intravenous administration show that the pharmacokinetics of the unchanged drug is not affected by ethylene-

Table 2 Pharmacokinetic parameters in healthy male volunteers (n=6) after intravenous infusion of 5 mg/kg of theophylline and of an equivalent dose of aminophylline (5.9 mg/kg).

Pharmacokinetic parameters	*Theophylline*		*Aminophylline*	
	Mean	*Range*	*Mean*	*Range*
Elimination constant, k_{el} (h^{-1})	0.209	0.140–0.312	0.222	0.147–0.282
Elimination half-life, $T_{½}$ (h)	4.9	2.9–6.6	4.7	2.8–6.4
Volume of distribution, $V_{d\beta}$ (l/kg)	0.47	0.43–0.52	0.48	0.43–0.52
Total clearance, Cl_{tot} ($l\,kg^{-1}\,h^{-1}$)	0.075	0.048–0.125	0.077	0.056–0.130

Table 3 Per cent binding of theophylline to serum proteins in healthy male volunteers (n=6), 20 min and 3 h after infusion of theophylline and aminophylline (5 mg/kg pure theophylline).

Time	*Theophylline*		*Aminophylline*	
	Mean	*Range*	*Mean*	*Range*
20 min	58	48–62	57	49–62
3 h	66	62–70	62	53–73

diamine. Concomitant administration of theophylline and allopurinol has been reported to induce a shift in theophylline metabolism without affecting the overall pharmacokinetics of the drug (Grygiel, Wing, Farkas & Birkett, 1979). Therefore, our finding of almost identical time course of unchanged theophylline concentration in serum with the test preparations does not rule out the possibility that ethylenediamine influences some metabolic pathways (Caldwell *et al.*, 1978).

The protein binding study suggests that ethylenediamine does not modify the free fraction of theophylline in serum. However, ultrafiltration is just one of several methods for the study of drug binding, and the filtrates were not entirely protein-free. Nevertheless, both of the parenteral solutions were tested in the same individuals and under identical conditions, and our values are close to those found in earlier studies with aminophylline (Simons *et al.*, 1979; Piafsky, Sitar, Rangno & Ogilvie, 1977).

Ethylenediamine is an allergen suspected of causing contract dermatitis in nurses and other professionals handling aminophylline tablets and suppositories (White *et al.*, 1978). Widespread dermatitis has also been described after intravenous administration of aminophylline in patients sensitized to ethylenediamine after using an antibiotic cream containing this compound as a stabilizer (Petrozzi & Shore, 1976; Provost & Jillson, 1967).

Ideally, since ethylenediamine has no desirable effect *in vivo* and it may be harmful in some patients, pure theophylline or preparations with pharmacologically inert additives should be preferred. Our absorption study and pharmacokinetic findings suggest that the oral and intravenous dosage schedules worked out for aminophylline also apply to pure theophylline, with appropriate correction for the contents of active drug in the preparations.

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