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Lack of effect of terfenadine on theophylline pharmacokinetics and metabolism in normal subjects

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The pharmacokinetics of oral theophylline (250 mg) and the production of its metabolites (3-methylxanthine, 1-methyluric acid, 1,3-dimethyluric acid) were studied before and after the administration of oral terfenadine (120 mg twice daily for 16 days) in 10 healthy volunteers. Comparison of volumes of distribution, elimination half-lives, areas under the plasma concentration-time curves, plasma clearance of theophylline and elimination of theophylline metabolites indicated that terfenadine had no significant effect on theophylline pharmacokinetics and metabolism.

Keywords theophylline terfenadine drug-interaction pharmacokinetics metabolism

Introduction

Classical antihistamines have been shown to inhibit bronchospasm induced by histamine or exercise and to have only a mild bronchodilator effect (Eiser *et al.*, 1981). However, the high doses required to produce such effects are associated with pronounced somnolence, limiting their use in therapy. Newer antihistamines, like terfenadine enable the value of H_1-receptor blockade in asthma to be reassessed since higher doses can be used without causing sedative side effects (Moser & Huther, 1978; Brandon & Weiner, 1980).

Terfenadine has been shown to have a bronchodilator effect in asthmatic subjects (Patel, 1984; Patel & Kerr, 1985). In bronchial challenge tests, terfenadine gave virtually complete protection against inhaled histamine (Rafferty & Holgate, 1987) and some inhibition of antigen-induced bronchoconstriction (Chan *et al.*, 1986). Furthermore, increased airway resistance induced by exercise (Patel, 1984) or isocapnic hyperventilation (Badier *et al.*, 1988) was effectively antagonised by terfenadine. Finally, Taytard *et al.* (1987) demonstrated a significant action of terfenadine 120 mg twice daily on the symptoms of mild allergic asthma in fifty two patients.

Since terfenadine may at times be administered to asthmatic patients requiring concomitant bronchodilator therapy with theophylline, any effect of terfenadine on theophylline pharmacokinetics is of potential clinical importance.

The aim of this study was to determine the effect of terfenadine treatment on plasma theophylline pharmacokinetics and also on theophylline metabolite formation since it has recently been shown that studies on the production and excretion of theophylline metabolites (3-methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid) provide useful information for exploration of two of the oxidative pathways mediated by cytochrome P-450, (*N*-demethylation and 8-hydroxylation) (Campbell *et al.*, 1987; Puurunen *et al.*, 1980; Grygiel *et al.*, 1984; Grygiel & Birkett, 1981; Naline *et al.*, 1988.)

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Methods

Subjects

Nine males aged 23 to 27 years (mean 24.7 ± 0.4 s.d.) weighing from 57 to 80 kg (mean 67 ± 2.2) and one female aged 26 years weighing 54 kg participated in the study.

All subjects had normal haematology and chemical pathology profiles and reported no history of allergy or adverse reaction to antihistamines or aminophylline. None took any other medication (including over-the-counter products) for 2 weeks before the study and until its completion. Alcohol, xanthine-containing food and beverages were prohibited from 24 h before each study day until the completion of blood sampling. Smokers were excluded from the study.

The study was conducted according to the Declaration of Helsinki as amended in Venice in 1983 and the protocol was approved by the local Medical Ethics Committee.

Protocol

The study proceeded in two stages. In stage I, the pharmacokinetic parameters relevant to theophylline metabolism under control conditions were determined. Each subject received a 250 mg dose of a fast-dissolving oral theophylline, i.e. two 125 mg tablets of Theolair® at 08.00 h after fasting overnight. Blood samples were collected in heparinized tubes 0.5, 1, 1.5, 2, 4, 6, 9, 12, 24 and 36 h after dosing, immediately centrifuged, then frozen and kept at −20° C pending assays of theophylline and its metabolites. Urine was collected in 4 samples: 0–4 h, 4–12 h, 12–24 h and 24–48 h; aliquots were stored at −20° C. 2 weeks later (stage II), terfenadine 240 mg, two tablets of 60 mg twice daily, was administered on 16 consecutive days; on the 14th day, the theophylline test as described above was performed.

Assays of theophylline and its metabolites

Theophylline and its metabolites were assayed by the h.p.l.c. method described by Naline *et al.* (1987).

Chromatography was carried out with a Varian 5000 instrument. UV detection was performed with a Spectroflow 773 (Kratos Analytical Instruments, Westwood, N.J. USA) set at 280 nm. A peak integrator CR-3A (Shimadzu Corporation, Kyoto, Japan) was used and automatic injections of 20 μl were made with a WISP injector (Waters Model 710 B autoinjector).

Stock dyphylline aqueous solution (100 μl) (as internal standard) and acetonitrile (200 μl) for protein precipitation were added to plasma (100 μl). After vortex mixing for 1 min and centrifugation at 3000 *g* for 5 min, the supernatant was transferred and evaporated to dryness under N_2 at 45° C. The residue was reconstituted with 100 μl of mobile phase and, after mixing, 20 μl were injected into the loop. Separation took about 15 min.

For urine assay, 300 μl of 1,9-DMU (1,9-dimethyluric acid) stock solution were added to a 1 ml urine sample, and a 400 μl aliquot of the mixture was purified on a C_{18} Sep-Pak column. After washing with 2 ml of 0.1 M sodium acetate buffer (pH 4.4), elution was performed with 1 ml of a mixture of 0.1 M sodium acetate buffer (pH 4.4) and acetonitrile (80–20 v/v). 20 μl of eluate were then injected into the chromatograph and the Sep-Pak column was washed with methanol (5 ml) and distilled water (5 ml) before re-use. Recoveries were 80% for 1,3-DMU (1,3-dimethyluric acid), 75% for theophylline, 75% for 3-MX (3-methylxanthine) and 66% for 1-MU (1-methyluric acid).

Calculation of pharmacokinetic parameters

For each subject, the elimination rate constant λ_z describing the terminal phase of theophylline elimination was calculated by the least squares method from the log plasma drug concentration *vs* time curves. The corresponding half-life ($t_{\frac{1}{2}.z}$) was calculated as:

$$t_{\frac{1}{2}.z} = \frac{0.693}{\lambda_z} \quad (1)$$

The area under the curve (AUC) was determined by the trapezoidal method extrapolated to infinity by dividing the last observed concentration by the terminal rate constant.

Theophylline clearance was calculated from the equation:

$$CL = \frac{D}{AUC} \quad (2)$$

where D is the dose administered.

The bioavailability of theophylline (Theolair®) was considered as being 100% (Jonkman *et al.*, 1979).

The volume of distribution was calculated as:

$$V = \frac{CL}{\lambda_z} \quad (3)$$

Partial metabolic clearances were calculated according to Miners *et al.* (1985)

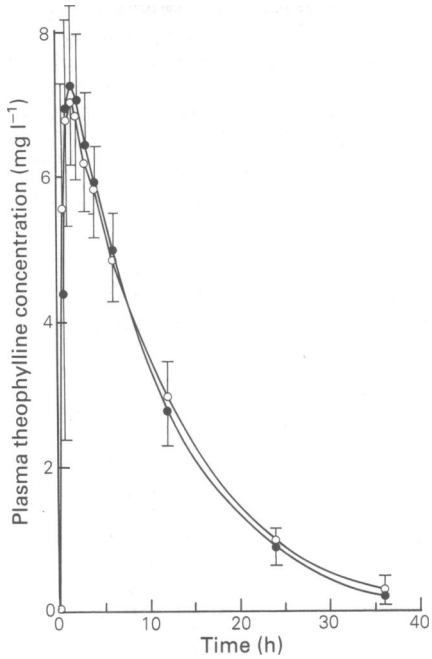

Figure 1 Mean ± s.d. plasma theophylline concentrations in 10 normal subjects following administration of theophylline 250 mg alone (•) and after treatment with terfenadine (120 mg twice daily for 16 days) (○).

$$CL_m = \frac{Ae\{m(0,48)\}}{AUC\ (0,48)} \qquad (4)$$

where $Ae\{m(0,48)\}$ is the amount of theophylline metabolite (m) excreted in the 0–48 h urine and AUC (0,48) is the area under the curve (0–48 h) of plasma theophylline concentrations. In this calculation, $Ae\{m(0,48)\}$ and AUC (0,48) were both expressed in molar units.

The renal clearance of theophylline was calculated from the amount excreted in 48 h divided by AUC at 48 h.

Expression of results and statistical analysis

The results in the text and table are expressed as means ± s.d.

Statistical analysis of the results was performed using Student's *t*-test for paired data.

Drugs

The drugs used were terfenadine (Teldane®, Merrell Dow Cie) and theophylline (Theolair 125®, Riker 3M).

Results and discussion

Plasma theophylline concentrations averaged over 10 subjects were plotted against time (Figure 1). No significant difference was observed before and after treatment with terfenadine 240 mg daily for 16 days.

Pharmacokinetic analysis of plasma theophylline and urine metabolites is presented in Table 1. Compared with control values, plasma theophylline half-life, AUC, clearance and volume of distribution remained unchanged after treatment with terfenadine. The amounts of theophylline and its metabolites—3-methylxanthine (3-MX), 1-methyluric acid (1-MU) and 1,3-dimethyluric acid (1,3-DMU) recovered in the 48 h urine and the clearance to these metabolites were also not modified by terfenadine.

In previous studies, the same protocol has disclosed pharmacokinetic interactions between theophylline and cimetidine or troleandomycin, and confirmed the absence of interaction with ketoconazole (Naline *et al.*, 1988). This further validates the results obtained in the present study.

Thus, this study did not demonstrate any influence of high oral doses of terfenadine on the pharmacokinetics of theophylline. Furthermore, no effect of terfenadine was shown on the partial clearance of theophylline by *N*-demethylation and 8-hydroxylation.

Table 1 Pharmacokinetic parameters of theophylline and its metabolites after administration of oral theophylline 250 mg before and after oral terfenadine (120 mg twice daily for 16 days) in 10 normal subjects. % is percentage of the amount excreted *vs* oral theophylline dose administered. The results are expressed as means ± s.d.

Parameters	*Control values*	*Values after treatment with terfenadine*
Theophylline		
$t_{½,z}$ (h)	7.19 ± 1.48	7.67 ± 1.84
V (l)	29.6 ± 5.7	30.4 ± 7.2
AUC (0–48 h) (mg l^{-1} h)	82.2 ± 20.0	84.5 ± 24.3
AUC (mg l^{-1} h)	86.1 ± 23.2	89.0 ± 26.9
CL (ml min^{-1})	49.2 ± 13.2	47.3 ± 10.8
CL_R (ml min^{-1})	8.8 ± 2.3	8.6 ± 1.7
Amounts excreted in 48 h urine		
3-MX (mg)	31.6 ± 9.5	30.0 ± 6.9
(mmol)	0.190 ± 0.057	0.180 ± 0.045
%	12.6 ± 3.8	12.0 ± 2.7
1-MU (mg)	51.0 ± 9.1	48.6 ± 9.2
(mmol)	0.280 ± 0.050	0.267 ± 0.051
%	20.4 ± 3.6	19.4 ± 3.7
1,3-DMU (mg)	92.5 ± 11.3	83.3 ± 15.1
(mmol)	0.471 ± 0.058	0.424 ± 0.077
%	37.0 ± 4.5	33.3 ± 6.0
Theophylline (mg)	42.1 ± 9.9	42.6 ± 11.0
(mmol)	0.234 ± 0.055	0.237 ± 0.061
%	16.8 ± 4.0	17.1 ± 4.4
Partial clearance to metabolites		
$CL_{3\text{-}MX}$ (ml min^{-1})	7.5 ± 3.4	6.9 ± 2.7
$CL_{1\text{-}MU}$ (ml min^{-1})	11.0 ± 4.2	10.2 ± 3.7
$CL_{1,3\text{-}DMU}$ (ml min^{-1})	18.3 ± 5.9	16.4 ± 6.1

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