The effect of tocainide on theophylline metabolism

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The effect of 5 days of oral tocainide (400 mg every 8 h) on the kinetics of theophylline given as a single 5 mg kg⁻¹ i.v. infusion over 30 min was investigated in eight healthy male nonsmokers. Treatment with tocainide decreased the plasma clearance of theophylline from 37.5 ± 6.9 (mean ± s.d.) to 33.7 ± 5.0 ml kg⁻¹ h⁻¹ (difference -3.8, 95% CI, -1.7 to -5.9; *P* = 0.004) and increased its terminal elimination half-life from 9.7 ± 2.5 to 10.4 ± 2.1 h (difference 0.7, 95% CI, 0.2 to 1.2; *P* = 0.011). Tocainide decreased the formation clearances of 3-methylxanthine and 1-methyluric acid, but the formation clearance of 1,3-dimethyluric acid was unaltered. These data indicate that tocainide exerts a modest inhibitory effect on theophylline metabolism. The magnitude of this change is substantially smaller than that reported to be produced by mexiletine.

Keywords tocainide theophylline metabolism drug interactions

Introduction

It is well recognized that the metabolism of theophylline can be perturbed by coadministration of other agents that modify the activities of selected cytochrome P450 (CYP) isoenzymes (Upton, 1991). Recent studies have shown that the antiarrhythmic agent mexiletine lowers the plasma clearance of theophylline by 40–45% and increases its half-life by a factor of 2 (Hurwitz *et al.*, 1991; Loi *et al.*, 1991; Stoysich *et al.*, 1991). A preferential inhibition of the demethylation of theophylline metabolism has also been shown (Hurwitz *et al.*, 1991; Loi *et al.*, 1991). Because the chemical structure of mexiletine is similar to that of tocainide (Figure 1), it is possible that tocainide also may influence the metabolism of theophylline. Therefore, we investigated the effect of tocainide on theophylline metabolism in young, healthy male nonsmokers.

Methods

Subjects

Eight male nonsmokers, aged 19 to 40 years, volunteered for this study, which was approved by the Research and Development Committee of the Boise Veterans Affairs Medical Center and the Human Subjects Review Committee of the University of Washington. Each subject gave written informed consent.

A complete history, physical examination, and routine

Figure 1 Chemical structures of tocainide and mexiletine.

laboratory tests that included a 12-channel chemistry screen, complete blood count, urinalysis, and electrocardiogram were performed on each subject. None had evidence of cardiac, renal, or hepatic dysfunction. All subjects abstained from alcohol for at least 1 week prior to the beginning of the study and were receiving no other medications during the study.

Protocol

The study lasted for 17 days and the subjects participated as outpatients. During this period, all subjects abstained from alcohol, dietary methylxanthines, charcoal-broiled meat, broccoli, Brussels sprouts, and cabbage. A baseline single-dose pharmacokinetic study of theophylline was performed on day 8. Subjects fasted overnight. At 07.00 h each subject assumed a recumbent position, and an indwelling Teflon cannula with an obturator (20-gauge, Deseret Medical Inc., Sandy, Utah) was inserted into an antecubital or forearm vein for serial blood sampling. A second cannula was inserted into a contralateral forearm vein for administration of theophylline. After blood samples were obtained for assay calibration, 5 mg kg⁻¹ theophylline in 5% w/v dextrose solution was infused over 30 min using a Harvard model 2205 pump fitted with a model 552 pump-speed modulator with high-resolution variable-speed controller (Devices for Medicine, Fairfax, VA). Serial 10 ml blood samples were collected at 10, 20, 30, 35, and 50 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 23, and 24 h after infusion was begun. An additional 10 ml sample was drawn after 1 h for the measurement of the plasma binding of theophylline. The blood samples were centrifuged immediately and the plasma was stored at -20° C until analysis. Subjects remained recumbent for 2 h after they received theophylline, and only minimal activity was permitted until collection of blood samples was complete. Urine samples were collected over 48 h after starting the infusion of theophylline. Boric acid was added to the urine samples to maintain pH at 5.5 and aliquots were stored at -20° C until analysis.

On day 10, the subjects began taking 400 mg tocainide every 8 h for 7 days. On day 15, a second single-dose pharmacokinetic study of theophylline was performed as described above except that tocainide was administered to the subjects at the beginning of theophylline infusion. Because the time course of recovery from the inhibitory effect of tocainide was not known, the sequence of theophylline pharmacokinetic studies was not randomized. The protocol was completed at 07.30 h on day 17. Adherence to a methylxanthine-free diet during the study was confirmed by analysis of pre-dose plasma and urine for caffeine, theobromine, and their metabolites.

Analytical methods

Plasma theophylline was measured by h.p.l.c. (Vestal *et al.*, 1983). At a concentration of 2 µg ml⁻¹, the interassay coefficient of variation was 7.4%. Urinary concentrations of theophylline and its metabolites (3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid) were determined by the method of Muir *et al.* (1980) with β-hydroxyethyl theophylline as the internal standard. At concentrations of 5 µg ml⁻¹ (3-methylxanthine), 4 µg ml⁻¹ (1-methyluric acid), and 8 µg ml⁻¹ (1,3-dimethyluric acid) the interassay coefficients of variation for these metabolites were 12.4%, 6.5%, and 7.1%, respectively. The plasma binding of theophylline was measured by equilibrium dialysis and liquid scintillation spectrometry after addition of radiolabelled drug to the samples (Cusack *et al.*, 1985).

Plasma tocainide was measured by a modification of

the method of vasBinder & Annesley (1991). Plasma (0.5 ml) was extracted with 5 ml methylene chloride after addition of 1.5 µg *N*-propionylprocainamide as internal standard, and 0.1 ml 0.5 M sodium carbonate. The samples were shaken for 15 min and centrifuged for 10 min at 2000 rev min⁻¹. The supernatant was aspirated and 0.5 ml 0.01 M hydrochloric acid was added to the methylene chloride. After shaking for 5 min, the tubes were centrifuged. A 40 µl volume of the top acid layer was injected onto the chromatograph. A Waters chromatographic system (Millipore Waters Associates, Milford, MA) consisting of a model 510 pump, a sample processor (WISP 710B), and a variable wavelength detector (model 490) set at 210 nm were used together with a NovaPak cyano HP column (5 × 100 mm) in a RCM compression module (Millipore Waters Associates, Milford, MA). The mobile phase consisted of 1 mM acetate buffer with 0.05% (v/v) triethylamine and 10% acetonitrile v/v (final pH 6.0) at a flow rate of 1.5 ml min⁻¹. At a concentration of 2.5 µg ml⁻¹, the interassay coefficient of variation was 6.2%.

Pharmacokinetic analysis

The elimination half-life (*t*_{1/2,z}) of theophylline was calculated from the rate constant, λ_z, determined by least squares regression of the log plasma drug concentrations in the terminal phase. Values of AUC for theophylline were determined using the linear trapezoidal rule with extrapolation to infinity. The plasma clearance (CL) of theophylline was calculated from dose/AUC and the volume of distribution (*V*) from dose/(AUC·λ_z). The formation clearances (CL_m) of the metabolites from theophylline were calculated from *f*_m·CL where *f*_m is the molar fraction of each individual metabolite recovered in the urine. The renal clearance (CL_R) of theophylline was calculated from *f*_e·CL where *f*_e is the molar fraction of theophylline excreted in the urine. The AUC for tocainide over a dosing interval (τ) was determined by the linear trapezoidal rule. The mean steady state plasma concentration (*C*_{av}) of tocainide was calculated from AUC/τ.

Statistical analysis

Data are expressed as mean values ± s.d. Mean differences with 95% confidence intervals (CI) also are reported. Statistical comparisons were made by use of the Student's paired two-tailed *t*-test. A *P* value of <0.05 was considered significant.

Results

The tocainide dosage regimen was well tolerated and produced a mean steady state plasma concentration of 4.6 ± 1.4 µg ml⁻¹. Tocainide lowered the plasma clearance of theophylline by 10% (95% CI, -4.2 to -14.4%) from a control value of 37.5 ± 6.9 ml kg⁻¹ h⁻¹ to 33.7 ± 5.0 (difference -3.8, 95% CI, -1.7 to -5.9; *P* = 0.004), while its volume of distribution and plasma free fraction were unaltered. The elimination half-life was prolonged slightly from 9.7 ± 2.5 h to 10.4 ± 2.1

Table 1 Parameters describing the kinetics and metabolism of theophylline with and without the coadministration of tocainide

	CL (ml kg ⁻¹ h ⁻¹)	t _{1/2} (h)	V (l kg ⁻¹)	Free fraction	Formation clearance*			Theophylline renal clearance*
					3-MX	1-MU	1,3-DMU	
Control	37.5 ± 6.9	9.7 ± 2.5	0.50 ± 0.04	0.56 ± 0.03	64.3 ± 15.5	100.2 ± 20.1	142.2 ± 30.9	68.2 ± 16.9
Tocainide	33.7 ± 5.0	10.4 ± 2.1	0.49 ± 0.03	0.57 ± 0.03	54.4 ± 11.9	85.4 ± 17.2	131.1 ± 21.4	66.2 ± 9.9
Mean difference	-3.8 ± 2.5	0.7 ± 0.6	-0.01 ± 0.02	0.01 ± 0.02	-9.9 ± 5.0	-14.8 ± 7.6	-10.9 ± 15.6	-2.0 ± 13.1
(95% CI)	(-1.7 to -5.9)	(0.2 to 1.2)	(0.0 to 0.03)	(0.0 to 0.03)	(-5.7 to -14.1)	(-8.4 to -21.2)	(2.1 to -23.9)	(-8.9 to 12.9)
P value	0.004	0.011	NS	NS	0.0008	0.0009	NS	NS

Data shown are mean ± s.d. (n = 8).

3-MX, 3-methylxanthine; 1-MU, 1-methyluric acid; 1,3-DMU, 1,3-dimethyluric acid; 95% CI, 95% confidence intervals for the mean difference;

NS, not statistically significant.

*Values expressed as l kg⁻¹ h⁻¹ × 10⁻⁴

(difference 0.7, 95% CI, 0.2 to 1.2; $P = 0.011$) (Table 1). The formation clearances to 3-methylxanthine and 1-methyluric acid were decreased by $15.0 \pm 6.6\%$ (95% CI, -11.5 to -19.5%) and $14.5 \pm 6.2\%$ (95% CI, -9.0 to -15.8%), respectively, while that to 1,3-dimethyluric acid was unaltered. The renal clearance of theophylline was unaffected by tocainide treatment.

Discussion

Tocainide is eliminated mostly by renal excretion as unchanged drug and by glucuronidation of a carbaminic acid derivative (Elvin *et al.*, 1980), whereas mexiletine undergoes glucuronidation and hydroxylation (Grech-Belanger *et al.*, 1985). The latter pathway of mexiletine metabolism may be mediated by CYP2D6 (Inaba *et al.*, 1985). In a previous study, we demonstrated that in young male and female nonsmokers, a mean steady-state plasma mexiletine concentration of $0.78 \mu\text{g ml}^{-1}$ ($4.4 \mu\text{M}$) is associated with a lowering of the clearance of theophylline by 40–45% (Loi *et al.*, 1991). By comparison, in the present study a mean steady-state plasma tocainide concentration of $4.6 \mu\text{g ml}^{-1}$ ($23.9 \mu\text{M}$), which is at the lower end of the therapeutic range, was associated with only a 10% decrease. Thus, mexiletine appears to be a much more potent inhibitor of theophylline elimination than tocainide. Like mexiletine, tocainide also has a selective inhibitory effect on the *N*-demethylation pathways of theophylline (Hurwitz *et al.*, 1991; Loi *et al.*, 1991).

In humans, the demethylation of theophylline is mediated primarily by CYP1A2 (McManus *et al.*, 1988; Robson *et al.*, 1988; Sarkar *et al.*, 1992). Because mexiletine exerts a greater impairment of the formation of the demethylated metabolites than tocainide, it can be inferred that mexiletine may have a greater affinity for this isoenzyme. This is consistent with an *in vitro* study showing that in liver microsomes from 3-methylcholanthrene-induced rats, tocainide is substantially less potent than mexiletine in impairing the activity of the CYP1A family of isoenzymes (Wei *et al.*, 1993).

In conclusion, we have shown that the administration of tocainide at a clinically relevant dose results in a modest and selective impairment in theophylline metabolism. However, the extent of this effect is unlikely to require any adjustment in theophylline dosage. Tocainide and mexiletine may be useful probes to investigate the interaction of foreign compounds with the cytochrome P4501A family of isoenzymes.

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