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Individual and combined effects of cimetidine and ciprofloxacin on theophylline metabolism in male nonsmokers

CHO-MING LOI[1,2], BEVERLY M. PARKER,[1], BARRY J. CUSACK[1,3] & ROBERT E. VESTAL[1,3,4]
[1]Clinical Pharmacology and Gerontology Research Unit, Department of Veterans Affairs Medical Center, Boise, ID 83702; [2]Department of Pharmacy Practice, College of Pharmacy, Idaho State University, Pocatello, ID 83209; Departments of [3]Medicine and [4]Pharmacology, University of Washington, Seattle, WA 98195, USA

1 The individual and combined effects of cimetidine and ciprofloxacin on theophylline metabolism were examined in six young male nonsmokers.
2 Treatment sequence consisted of 7 days each of cimetidine 400 mg p.o. every 12 h, ciprofloxacin 500 mg p.o. every 12 h, and the combination of cimetidine and ciprofloxacin.
3 Studies of theophylline pharmacokinetics were performed at baseline and on the fifth day of each regimen.
4 Individually, cimetidine and ciprofloxacin decreased the clearance of theophylline by 25% and 32%, respectively. Therapy with the combined regimen resulted in a 41% reduction in theophylline clearance, which was greater than that achieved with each drug alone ($P < 0.01$).
5 Ciprofloxacin, in contrast to cimetidine, inhibited *N*-demethylations of theophylline to a significantly greater extent than the hydroxylation pathway. Combined treatment produced a further decline in formation of 1,3-dimethyluric acid than each drug alone.
6 These data suggest that coadministration of cimetidine and ciprofloxacin exerts a greater impairment of theophylline biotransformation than each inhibitor alone. The enhanced inhibitory effect from the two inhibitors will occur only when sub-maximal doses of each individual agent are used.

Keywords cimetidine ciprofloxacin drug interactions theophylline drug metabolism humans

Introduction

Theophylline is a methylxanthine bronchodilator frequently prescribed in the treatment of asthma and chronic obstructive pulmonary disease. The elimination of this drug involves *N*-demethylations to form 3-methylxanthine and 1-methylxanthine, which is further metabolized to 1-methyluric acid by xanthine oxidase, and 8-hydroxylation to form 1,3-dimethyluric acid [1–3]. These metabolic reactions are catalyzed by selective isozymes of the cytochrome P450 system [4–6].

Although many studies have examined the influence of a single inhibitor on the metabolism of theophylline, there is limited information on drug interactions involving theophylline and multiple inhibitors of hepatic drug metabolism. Using cimetidine and ciprofloxacin as model compounds, a recent study indicates that coadministration of a maximally inhibiting dose of cimetidine (2400 mg daily) and a therapeutic dose of ciprofloxacin (500 mg twice daily) produced a further reduction in theophylline clearance compared with ciprofloxacin alone, but not with cimetidine alone [7]. However, the inhibitory effect of cimetidine on hepatic drug metabolism is dose-dependent [8], and the standard therapeutic dose of cimetidine (800 mg daily) is substantially lower than the maximally inhibiting dose of 2400 mg daily. It is possible that concomitant administration of a therapeutic dose of both ciprofloxacin and cimetidine may have a different effect on inhibition of theophylline metabolism. Furthermore, the effect of this combined regimen on formation of theophylline metabolites has not been characterized. Accordingly, the purposes of this study were to investigate the effect of coadministration of a therapeutic dose of cimetidine and ciprofloxacin on

Correspondence and request for reprints: Dr Robert E. Vestal, Research Service (151), VA Medical Center, 500 W. Fort Street, Boise, ID 83702, USA

the metabolism of theophylline, and to elucidate the combined effect of these inhibitors on the metabolic pathways of theophylline.

Methods

Subjects

Six healthy male nonsmokers, age 22 to 35 years, volunteered for this study. The protocol was approved by the Research and Development Committee of the Boise VA Medical Center and the Human Subjects Review Committee of the University of Washington. Volunteers gave informed written consent after full explanation of the procedures and risks of the study.

A complete history, physical examination, and routine laboratory tests that included a 12-channel chemistry screen, electrocardiogram, complete blood count, and urinalysis were performed in each subject. None of the subjects had evidence of cardiac, renal, or hepatic dysfunction. Subjects received no other medications during the study. All subjects abstained from alcohol, dietary methylxanthines, charcoal-broiled meat, broccoli, Brussels sprouts, and cabbage for at least 1 week prior to and throughout the study.

Protocol

An outline of the study protocol is shown in Figure 1. The baseline single-dose pharmacokinetic study of theophylline was performed on day 1. 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, UT) 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 standard curve preparation, 5 mg kg^{-1} of theophylline in 5% w/v dextrose (Kendall McGaw Laboratories, Inc., Irvine, CA) was infused over 30 min (Harvard model 2205 infusion pump fitted with a model 552 pump-speed modulator and high-resolution variable-speed controller; Devices for Medicine, Fairfax, VA). Serial blood samples (10 ml each) were collected at 10, 20, 30, 35, and 50 min and at 1, 1.5, 3, 4, 6, 9, 12, 23, 24 and 48 h after infusion was begun. An additional 10 ml sample was drawn after 1 h for measurement of the plasma protein of theophylline. Blood samples were centrifuged immediately, and the plasma was stored at −20° C until analysis. Subjects remained in the recumbent position for 2 h after they received theophylline and only minimal activity was permitted until completion of blood sampling. Urine samples were collected over 72 h. Boric acid was added to the urine samples to maintain a pH of 5.5. The total volume of the urine samples was measured, and aliquots were stored at −20° C until analysis.

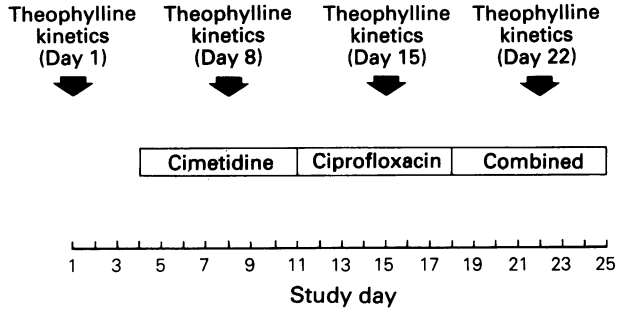

Figure 1 Protocol to investigate the effect of cimetidine and ciprofloxacin individually and in combination on theophylline metabolism.

Beginning on day 4, each subject received the following: (1) cimetidine 400 mg orally every 12 h for 7 days (study days 4–10), (2) ciprofloxacin 500 mg orally every 12 h for 7 days (study days 11–17), and (3) cimetidine 400 mg every 12 h and ciprofloxacin 500 mg orally every 12 h for 7 days (study days 18–24). Single-dose pharmacokinetic studies of theophylline were repeated on the fith day of each treatment regimen (study days 8, 15, and 22). Procedures for the studies were the same as on day 1, except that the appropriate study medication was administered to the subjects at the beginning of theophylline infusion. Blood and urine samples were collected as described previously.

Drug assay and pharmacokinetic analysis

Theophylline concentrations in plasma were measured by high performance liquid chromatography [9] with an interassay coefficient of variation of 7.4% at a concentration of 2 μg ml^{-1}. Experiments were performed to confirm that cimetidine and ciprofloxacin do not interfere with this assay. Measurement of plasma protein binding was done using liquid scintillation spectrometry after equilibrium dialysis [10]. Urinary concentrations of theophylline and its metabolites (3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid) were determined by the ion- pair gradient elution method of Muir *et al.* [11] with β-hydroxyethyl theophylline as the internal standard. The interassay coefficients of variation for these metabolites were 12.4%, 6.5%, and 7.1% at concentrations of 5 μg ml^{-1} (3-methylxanthine), 4 μg ml^{-1} (l-methyluric acid), and 8 μg ml^{-1} (1,3-dimethyluric acid), respectively. Although metabolites of cimetidine and ciprofloxacin were not available to evaluate possible interference with the h.p.l.c. assay of theophylline and its metabolites, baseline plasma and urine samples prior to each theophylline kinetic study did not show peaks that interfered with the analytes of interest.

The unweighted plasma concentrations of theophylline during the terminal elimination phase were fitted using a non-linear, least-square regression program to calculate the terminal elimination rate constant (λ_z). The terminal elimination half-life ($t_{½,z}$) of theophylline was calculated from $0.693/\lambda_z$. AUC values were estimated using the linear trapezoidal rule and theophylline clearance (CL) was calculated from D/AUC. The volume of distribution (V_{area}) was calculated from $D/(AUC \cdot \lambda_z)$. The formation clearances (CL_m) of the metabolites from theophylline were calculated from $fm \cdot CL$, where f_m is the molar fraction of the administered dose eliminated from the body as a given metabolite. The renal clearance (CL_R) of theophylline was calculated from $fe \cdot CL$, where f_e is the molar fraction of theophylline recovered in the urine.

Statistical analysis

Data are expressed as the mean ± s.e. mean. Values for 95% confidence intervals (95% CI) are also provided. Statistical comparisons were made using two-way ANOVA with Duncan's new multiple range test. A P value of <0.05 was considered to be significant.

Results

The effects of cimetidine and ciprofloxacin on the pharmacokinetics of theophylline are summarised in Table 1. The elimination of theophylline declined significantly during all three treatment periods. When administered individually, cimetidine decreased the plasma clearance of theophylline from 49.0 ± 4.9 to 36.5 ± 3.4 ml h^{-1} kg $^{-1}$ ($P < 0.01$), while ciprofloxacin lowered the plasma clearance of theophylline to 33.2 ± 3.1 ml h^{-1} kg^{-1} ($P < 0.01$). Combined administration of cimetidine and ciprofloxacin resulted in a further decline in theophylline clearance to 28.8 ± 2.6 ml h^{-1} kg^{-1}, which was lower than that during the cimetidine treatment phase ($P < 0.01$) as well as during the ciprofloxacin treatment period ($P < 0.05$). In reciprocal fashion, the elimination half-life of theophylline was prolonged from 7.2 ± 0.6 to 10.2 ± 0.7 h ($P < 0.01$) with cimetidine, and to 10.6 ± 0.7 h ($P < 0.01$) with ciprofloxacin. During the combined treatment phase, the elimination half-life of theophylline was increased to 12.8 ± 0.9 h, which was significantly different from baseline as well as from the cimetidine phase and the ciprofloxacin phase. The free fraction and the volume of distribution of theophylline were not altered by any of the treatment regimens.

Coadministration of cimetidine and ciprofloxacin was associated with a greater proportionate decline in clearance of theophylline compared with each agent alone (Figure 2). The proportionate reduction was 40.9 ± 2.1% (95% CI, 35.5–46.3) with the combined regimen, compared with 25.3 ± 1.9% (95% CI, 20.4–30.2) during cimetidine treatment ($P < 0.01$) and 32.1 ± 1.8% (95% CI, 27.5–36.7) during ciprofloxacin therapy ($P < 0.01$).

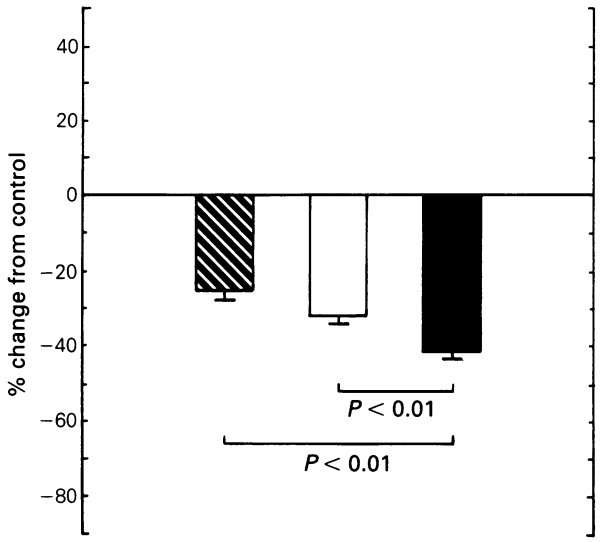

Figure 2 Effects (mean ± s.e. mean) of cimetidine (▨) and ciprofloxacin (□) alone and in combination (■) on theophylline clearance.

Likewise, the proportionate increase in theophylline elimination half-life was 77.8 ± 6.1% (95% CI, 62.1–93.5) with the combined treatment, which was markedly higher than that achieved with cimetidine alone (42.3 ± 3.7%; 95% CI, 32.8–51.8; $P < 0.01$) and with ciprofloxacin alone (48.0 ± 3.7%; 95% CI, 38.5–57.5; $P < 0.01$).

The effects of cimetidine and ciprofloxacin on the formation clearance of theophylline metabolites are summarized by the data shown in Table 2. The urinary recovery of theophylline and its metabolites averaged 88%. Both agents, when administered individually, significantly decreased the formation of all theophylline metabolites. Coadministration of cimetidine and ciprofloxacin was associated with a further decrease in the formation of 1,3-dimethyluric acid when compared with each agent alone. The combined regimen lowered the formation clearance of 3-methylxantine and 1-methyluric acid to a significantly greater extent than cimetidine alone, but not compared with ciprofloxacin alone. The renal clearance of theophylline was unaltered by any of the treatment regimens.

Table 1 Effect of cimetidine and ciprofloxacin on theophylline pharmacokinetics

	Baseline	*Cimetidine*	*Ciprofloxacin*	*Cimetidine + Ciprofloxacin*
CL ($ml\ h^{-1}\ kg^{-1}$)	49.0 ± 4.9 (36.4–61.6)	36.5 ± 3.4* (27.8–45.2)	33.2 ± 3.1* (25.2–41.2)	28.8 ± 2.6*,†,‡ (22.1–35.5)
$t_{½,z}$ (h)	7.2 ± 0.6 (5.7–8.7)	10.2 ± 0.7* (8.4–12.0)	10.6 ± 0.7* (8.8–12.4)	12.8 ± 0.9*,†,§ (10.5–15.1)
V_{area} ($l^{-1}\ kg$)	0.47 ± 0.02 (0.42–0.52)	0.49 ± 0.03 (0.41–0.57)	0.47 ± 0.02 (0.42–0.52)	0.47 ± 0.02 (0.42–0.52)
Free fraction	0.54 ± 0.01 (0.51–0.57)	0.54 ± 0.01 (0.51–0.57)	0.54 ± 0.01 (0.51–0.57)	0.54 ± 0.01 (0.51–0.57)

Data shown are means ± s.e. mean with 95% CI in parentheses.
*$P < 0.01$ compared with baseline.
†$P < 0.01$ compared with cimetidine.
‡$P < 0.05$ compared with ciprofloxacin.
§$P < 0.01$ compared with ciprofloxacin.

Table 2 Effects of cimetidine and ciprofloxacin on the renal clearance of theophylline and formation clearances to its metabolites

	Formation clearance			
Group	*3-MX*	*1-MU*	*1,3-DMU*	*Theophylline renal clearance*
Baseline	86.5 ± 14.3 (49.7–123.3)	114.8 ± 14.6 (77.3–152.3)	220.5 ± 24.3 (158.0–283.0)	70.3 ± 4.6 (58.5–81.6)
Cimetidine	62.5 ± 9.5* (38.1–86.9)	80.2 ± 9.2* (56.6–103.8)	162.1 ± 18.6* (113.3–208.9)	60.0 ± 7.5 (40.7–79.3)
Ciprofloxacin	41.1 ± 5.8*,† (26.2–56.0)	60.7 ± 8.0*,† (40.1–81.3)	161.3 ± 18.4* (114.0–208.6)	68.3 ± 8.3 (47.0–89.6)
Cimetidine + Ciprofloxacin	33.9 ± 6.0*,† (18.5–49.3)	49.9 ± 7.3*,† (31.1–68.7)	136.3 ± 18.1*,†,‡ (115.5–157.1)	68.9 ± 3.7 (54.4–73.4)

Data (expressed as $l\ h^{-1}\ kg^{-1} \times 10^{-4}$) are means ± s.e. mean with 95% CI in parentheses.
3-MX, 3-methylxanthine; 1-MU, 1-methyluric acid; 1,3-DMU, 1,3-dimethyluric acid.
*$P < 0.05$ compared with baseline.
†$P < 0.05$ compared with cimetidine.
‡$P < 0.05$ compared with ciprofloxacin.

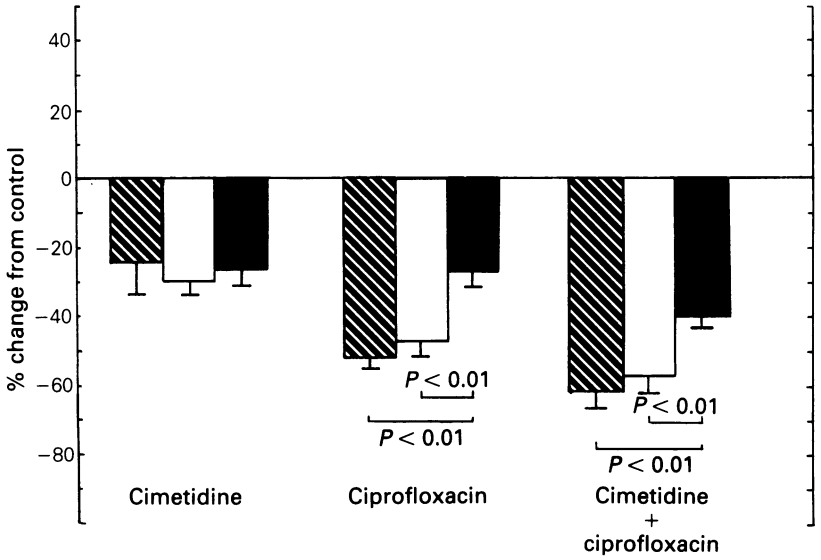

Figure 3 Effects (mean ± s.e. mean) of cimetidine and ciprofloxacin on the formation clearances of theophylline metabolites (▨ 3-MX, □ 1-MU, ■ 1,3-DMU).

The inhibitory effects of cimetidine and ciprofloxacin on individual metabolic pathways of theophylline elimination are shown in Figure 3. Cimetidine produced similar changes in the formation clearances of 3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid. In contrast, ciprofloxacin exerted a greater inhibitory effect on the demethylation than on the hydroxylation of theophylline. Thus, the percentage decreases in formation clearance of 3-methylxanthine and 1-methyluric acid were 51.4 ± 3.4 (95% CI, 42.7–60.1) and 46.9 ± 3.7 (95% CI, 37.4–56.4), respectively, which were substantially greater than that of 1,3-dimethyluric acid 26.5 ± 4.7 (95% CI, 14.4–38.6; $P < 0.01$). Concurrent administration of cimetidine and ciprofloxacin also resulted in a preferential inhibiton of the demethylation pathway as with ciprofloxacin alone. The proportionate decreases in formation clearance of 3-methylxanthine and 1-methyluric acid were 60.6 ± 4.9% (95% CI, 48.0–73.2) and 56.9 ± 4.7% (95% CI, 44.8–69.0), respectively, which were significantly greater than that of 1,3-dimethyluric acid (38.9 ± 2.9%; 95% CI, 31.4–46.4; $P < 0.01$).

Discussion

Our observations are in good agreement with the findings of other studies which demonstrate that, individually, cimetidine [10, 12, 13] and ciprofloxacin [14–16] inhibit the metabolism of theophylline by 25 to 35%.

We have also shown that cimetidine and ciprofloxacin impair both the demethylation and the hydroxylation of theophylline (Table 2). This finding is consistent with that reported by Vestal *et al.* [17] and provides further evidence that cimetidine is a nonselective inhibitor of

theophylline metabolism. In contrast, the observation that ciprofloxacin has a preferential inhibitory effect on the formation of 3-methylxanthine and 1-methyluric acid is in keeping with the results of other *in vivo* and *in vitro* studies [18, 19].

The proportionate lowering of theophylline clearance was greater during the combined treatment phase than with either cimetidine or ciprofloxacin alone (Figure 2). In contrast, Davis *et al.* [7] found that ciprofloxacin (500 mg twice daily) and a maximally inhibiting dose of cimetidine (2400 mg day^{-1}) decreased theophylline clearance more than when ciprofloxacin was given alone but not when cimetidine was given alone. This difference may be attributed to the differences in the daily dose of cimetidine employed in these studies indicating that when a maximally inhibitory dose of one drug is used, addition of a second inhibitor may have no further affect on the metabolism of theophylline.

The finding that the combined regimen produced a further decline in the formation of 1,3-dimethyluric acid when compared with each individual agent suggests that the partially additive inhibitory effects of the combined regimen on theophylline metabolism can be attributed, at least in part, to an enhanced inhibition of the hydroxylation pathway. With regard to demethylation, the combined treatment caused a slight increase in inhibition of the formation of 3-methylxanthine and 1-methyluric acid compared with ciprofloxacin alone. These data indicate that the inhibitory effects of the combined treatment on theophylline metabolism is qualitatively similar to that exerted by ciprofloxacin alone (Figure 3).

A limitation of this study was a lack of randomisation of the order of treatments. Therefore, it is not possible to exclude an effect due to carry over from one treatment period to the next. In particular, the inhibitory action of ciprofloxacin during the second treatment period of the study might have been influenced by a residual effect of cimetidine from the first treatment period. Since it takes only 48 h for plasma concentrations of theophylline to return to baseline after discontinuation of cimetidine [13], the 5 day treatment period was sufficiently long for the individual inhibitory effect of cimetidine to disappear prior to the measurement of theophylline kinetics on the fifth day of oral ciprofloxacin administration. Also, the individual inhibitory effects of cimetidine and ciprofloxacin in this study were similar to those reported previously [10,12–17]. Therefore, it seems unlikely that the results would have been substantially different if the treatment order had been randomized. In addition, a practical consideration is that the protocol for this study simulated the clinical situation in which another drug, in this case cimetidine, is added to an existing drug regimen, in this case ciprofloxacin.

In conclusion, this study demonstrated that cimetidine and ciprofloxacin, at standard therapeutic doses, are inhibitors of theophylline elimination. Their combined administration caused a proportionately greater decrease in theophylline clearance than that achieved with each agent alone. This less than fully additive effect can be attributed largely to an enhanced inhibition of the formation of 1,3-dimethyluric acid. In patients receiving theophylline together with several inhibitors, appropriate adjustment of theophylline dosage should be instituted based on the expected change in theophylline clearance as a result of the drug interaction and on plasma theophylline concentration measurements.

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