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The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects

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1 The mechanism of the interaction between ciprofloxacin and theophylline was investigated in nine healthy subjects.

2 Subjects were given a single oral dose of theophylline (3.4 mg kg^{-1}), before and after 60 h of ciprofloxacin therapy at a dose of 500 mg twice daily.

3 Ciprofloxacin reduced the oral clearance of theophylline by 19% (−7.73 ± 6.42 ml kg^{-1} h^{-1} (95% confidence limits −12.66, −2.79)). Some subjects (group A, n = 4) showed little decrease in clearance (mean 4.4%; −1.6 ± 0.7 ml kg^{-1} h^{-1} (−2.6, −0.5)), whereas others (group B, n = 5) showed a marked decrease (mean 30%; −12.7 ± 3.7 ml kg^{-1} h^{-1} (−17.2, −8.1)).

4 Comparing groups A and B, the decrease in oral clearance of theophylline in group B could not be ascribed to differences in the AUC of ciprofloxacin. Group A subjects showed only slight inhibition of 1-demethylation (−12.8 ± 5.5% (−21.5, −4.0)), while group B subjects showed a significantly greater inhibition of 1-demethylation (−49.9 ± 9.8% (−62.1, −37.7)), 3-demethylation (−44.8 ± 8.6% (−55.4, −34.1)) and 8-hydroxylation (−27.0 ± 3.7% (−31.6, −22.4)).

5 The results suggest that inter-individual variability in the inhibition of theophylline metabolism by ciprofloxacin can be attributed to inter-individual differences in the level of CYP1A2 expression and/or in the degree of inhibition of hepatic CYP1A2 and CYP3A4.

6 The interaction between ciprofloxacin and theophylline can be clinically significant. However, uniform decrease in the theophylline dose is not warranted because there is a negligible change in theophylline clearance when ciprofloxacin is co-administered in a substantial proportion of patients.

Keywords ciprofloxacin theophylline drug interactions humans pharmacokinetics

Introduction

The metabolic interaction between fluoroquinolones and theophylline is well documented [1, 2], with enoxacin and ciprofloxacin having a more potent inhibitory effect on the cytochrome P450 system than norfloxacin, ofloxacin and lomefloxacin [3, 4]. In the case of ciprofloxacin, studies have shown a 25–32% decrease in the clearance of theophylline [5–10], with an increase in elimination half-life of 42–51% [7, 9, 10]. There was no change in renal clearance of theophylline when it was co-administered with ciprofloxacin [7, 8, 11]. Clinical management of patients taking ciprofloxacin and theophylline is not defined clearly [5, 6, 12, 13], despite reports of substantially elevated plasma theophylline concentrations and deaths [1, 14–21].

Some previous studies have shown marked inter-individual variability in the effect of ciprofloxacin on theophylline pharmacokinetics. Raoof *et al.* [12] found a significant increase in plasma theophylline concentration in 61% of 33 patients, while the remaining 39% exhibited no change. Nix *et al.* [13] described a mean decrease in theophylline clearance

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of 17% when ciprofloxacin was co-administered, but this change was not statistically significant. However, three of their eight subjects showed a substantial decrease in theophylline clearance, ranging from 42% to 113% [13].

In the present study we have investigated the mechanism of the inter-individual variability and the extent of inhibition of theophylline metabolism by ciprofloxacin, after oral doses of both drugs.

Methods

Subjects and study design

Nine healthy, non-smoking volunteers participated in the study. Five were females (mean age = 26.4 years, range 19–36 years) and four males (mean age = 20.5 years, range 18–23 years). All subjects underwent a full medical examination 1 week prior to the study, including routine biochemical and haematological tests and a resting 12-lead electrocardiogram. One female subject was taking thyroxine and was clinically and biochemically euthyroid.

The study was approved by the Fremantle Hospital Research and Human Rights Committee. All subjects gave written, informed consent.

Subjects were required to stop consumption of caffeine-containing products 48 h prior to commencement of the study. On day 1 a single 3.4 mg kg^{-1} dose of theophylline syrup (Neulin®, 3M Pharmaceuticals Australia Pty Ltd), diluted with approximately 100 ml water, was administered orally after an overnight fast. Subjects continued to fast until 1.5 h after the theophylline dose, when a standard, light breakfast was provided. Venous blood samples (5 ml) were drawn at 0, 10, 20, 30, 45, 60 and 90 min, and 2, 3, 4, 6, 8, 10, 24 and 26 h after theophylline administration. The samples were collected in lithium heparin tubes (Vacutainer®, Becton Dickinson). Plasma was separated by centrifugation and stored at −20° C until assayed.

Urine was collected over 12 h periods for 36 h following the dose of theophylline. Boric acid solution 4% w/v (100 ml per container) was used during the sample collection to acidify the urine. The urine was combined and samples were stored at −20° C until analysed.

At the end of the 36 h urine collection period subjects began taking ciprofloxacin (Ciproxin®, Bayer) at a dose of 500 mg twice daily. On day 5, a second dose of theophylline was administered, followed by the same blood and urine sampling protocol as for day 1. Subjects continued to take ciprofloxacin for 24 h after their final blood sample. Adverse effects reported during each of the study periods were recorded.

Chemical analyses

Plasma theopylline was measured by fluorescence polarization immunoassay using TDx reagents and analyzer according to the Abbott TDx® protocol (Abbott Laboratories Diagnostic Division, North Chicago, Illinois, USA, April 1993). The plasma binding of theophylline was measured in the 2 h blood sample. The within-day coefficients of variation for the assay were 14.2, 4.2, 1.7, 1.3 and 1.1% at 0.5, 1, 2.5, 5 and 10 mg l^{-1} of theophylline, respectively. Protein binding was determined using Centrifree micropartition Filters (Amicon Scientific Australia). Plasma ultrafiltrates were prepared by centrifugation at 1000 *g* for 5 min in a 35° fixed angle rotor and theophylline concentrations were measured by the Abbott TDx method as above.

Urinary concentrations of theophylline (1,3-DMX) and its metabolites, 1-methyluric acid (1-MU), 3-methylxanthine (3-MX) and 1,3 dimethyluric acid (1,3-DMU) were measured by h.p.l.c. A 0.2 ml aliquot of urine and 0.05 ml of internal standard (1-methylxanthine; 5 μg) were added to a washed Bondelut SAX column (1 ml). The compounds were eluted with 1 volume of distilled water. Phosphate buffer pH 3 (0.5 ml), ammonium sulphate (1.8 g) and 25% v/v isopropanol in chloroform (8 ml) were added and the contents shaken for 5 min and then centrifuged for 3 min at 1500 *g*. A 7.5 ml aliquot of the organic phase was removed and dried under nitrogen. The residue was dissolved in 0.5 ml 0.02 M sodium hydroxide by sonication, and 0.01 ml aliquots were injected immediately onto the column. The assay used a Beckman Ultrasphere ODS column (25 cm × 4 mm i.d.) with a Biorad microguard clinical reversed phase cartridge and a solvent comprising 6% v/v methanol in 0.045% v/v acetic acid. The flow rate was 1.2 ml min^{-1} with detection by u.v. absorption at 280 nm. Results were interpolated from a standard curve run with each batch of samples. Preliminary analysis established that there were no detectable levels of endogenous 1-methylxanthine in any of the samples. The within-day coefficients of variation (n = 5) were: theophylline at 6.1 and 10.1 mg l^{-1}, 2.9% and 1.5%, respectively; 3-MX at 4.5 and 15.9 mg l^{-1}, 1.1% and 1.4%, respectively; 1-MU at 3.6 and 21 mg l^{-1}, 2.4% and 1.3%, respectively, and 1,3-DMU at 4.9 and 29 mg l^{-1}, 3.8% and 1.8%, respectively. Samples for both phases of the study for each volunteer were analysed on the same day.

Ciprofloxacin concentrations in plasma were measured by h.p.l.c. Plasma (0.2 ml) and 0.025 ml of internal standard (norfloxacin, 1 μg) were extracted with 5 ml 40% v/v acetonitrile in dichloromethane. The samples were centrifuged and the organic phase transferred to a clean polypropylene tube and taken to dryness under a stream of dry nitrogen. The residue was reconstituted in 0.2 ml of h.p.l.c. mobile phase by vortexing and sonicating and a 0.05 ml aliquot was injected onto the column. A Merck Lichrosphere 60 RP Select-B 5 μm column (25 mm × 4 mm i.d.) was used, with a mobile phase of 17% v/v acetonitrile and 0.05% v/v triethylamine in 0.1 M phosphoric acid (final pH 2.3). The solvent was pumped at a rate of 1.3 ml min^{-1} and the eluting peaks were detected by their u.v. absorbance at 313 nm. Unknown concentrations of ciprofloxacin were interpolated from a standard curve (0.2–3.5 mg l^{-1}) run with each batch of samples. The within-day

coefficient of variation for the assay ranged from 4.2% at 0.2 mg l^{-1} to 0.7% at 2.8 mg l^{-1} (n = 5).

Pharmacokinetic and statistical analyses

A one-compartment open model with first order absorption was fitted to the plasma theophylline concentration data by non-linear least squares regression. Estimates of the apparent absorption rate constant (k_a), elimination rate constant (k) and volume of distribution (V) were obtained. The elimination half-life ($t_{1/2}$) was calculated from 0.693/k. Values of AUC and AUMC were calculated as described by Rowland & Tozer [22]. Mean residence time (MRT) was calculated from AUMC/AUC and oral clearance (CL_o) from dose/AUC. The formation clearances (CL_m) of 1-MU, 3-MX and 1,3-DMU were calculated from $f_m \times CL_o$, where f_m is the molar urinary recovery of the respective metabolite as a fraction of the total recovery of drug plus metabolites. The renal clearance (CL_R) of theophylline was calculated from $f_e \times CL_o$, where f_e is the molar urinary recovery of theophylline as a fraction of the total recovery of theophylline plus metabolites. Data are summarised as mean ± s.d. Mean pharmacokinetic parameters were compared by use of a paired t-test. The 95% confidence limits for differences between means were calculated.

Results

The pharmacokinetic parameters of theophylline before and during ciprofloxacin treatment are summarized in Table 1. There were no significant changes in k_a, V or free fraction of theophylline after ciprofloxacin treatment. The oral clearance of theophylline was decreased by a mean of 19%, while its $t_{1/2}$ and MRT were increased by 26% and 28%, respectively. The total urinary recovery of theophylline and metabolites was decreased significantly ($P < 0.05$), from 84.6 ± 12.6% to 75.1 ± 11.7% by co-administration of ciprofloxacin.

In four of the subjects (group A) there was a mean 4.4% decrease (−1.6 ± 0.7 ml kg^{-1} h^{-1}; 95% CI −2.6, −0.5; P = 0.02) in clearance, compared with a mean 30% decrease (−12.7 ± 3.7 ml kg^{-1} h^{-1}; 95% CI −17.2, −8.1; P = 0.002) in the other five subjects (group B). Mean plasma concentrations in the two groups are shown in Figure 1a and b. There was a significant decrease in the oral clearance of theophylline in group B compared with group A (P = 0.001, Table 2). The formation clearances of 1-MU, 3-MX and 1,3-DMU, as well as the renal clearance of theophylline, are shown in Table 2.

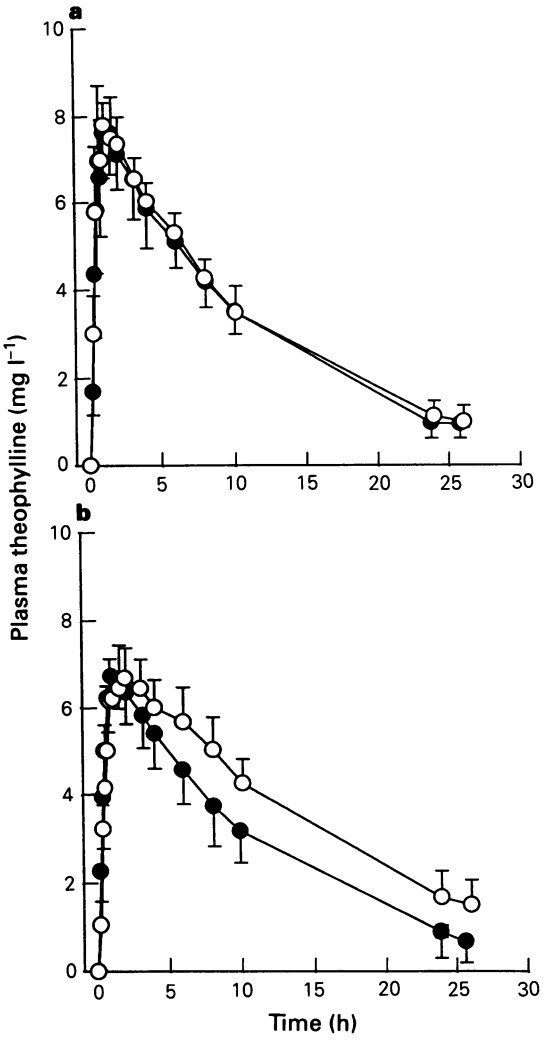

Figure 1 Plasma theophylline concentrations (mean ± s.d.) in the subjects of group A (a) (small change in CL_o) and group B (b) (large change in CL_o) before (●) and during (○) ciprofloxacin therapy.

Table 1 Pharmacokinetic parameters of theophylline before and during ciprofloxacin therapy

Parameter	*Theophylline*	*Theophylline plus ciprofloxacin*	*Difference*	*(%Δ)†*	*95% CI*
k_a (h^{-1})	2.16 ± 0.77	1.86 ± 0.75	−0.30 ± 0.81	(−14)	(−0.93, 0.32)
V (l kg^{-1})	0.42 ± 0.04	0.41 ± 0.04	−0.01 ± 0.02	(−2)	(−0.02, 0.01)
$t_{1/2}$ (h)	7.07 ± 1.01	8.86 ± 1.87	1.79 ± 1.50	(+26)*	(0.64, 2.94)
CL_o (ml kg^{-1} h^{-1})	39.48 ± 7.10	31.76 ± 5.43	−7.73 ± 6.42	(−19)*	(−12.66, −2.79)
MRT (h)	10.37 ± 1.76	13.33 ± 2.90	2.96 ± 2.67	(+28)*	(0.91, 5.01)
Free fraction in plasma	0.43 ± 0.06	0.44 ± 0.10	0.01 ± 0.10	(−2)	(−0.06, 0.10)

Data are shown as mean ± s.d. with 95% CI for the differences.
†Percentage change.
*$P \leq 0.01$.

Table 2 Changes in renal clearance of theophylline and formation clearance of metabolites for subjects showing small (group A) and large (group B) differences in inhibition of theophylline metabolism by ciprofloxacin

Subjects (% decrease CL_O of theophylline)	$CL_{1\text{-}MU}$				$CL_{3\text{-}MX}$				$CL_{1,3\text{-}DMU}$				$CL_{R(Theophylline)}$			
	T	*T+C*	*Difference*	*%Δ*	*T*	*T+C*	*Difference*	*%Δ*	*T*	*T+C*	*Difference*	*%Δ*	*T*	*T+C*	*Difference*	*%Δ*
Group A																
2 (−3.9)	5.9	6.3	0.4	7.4	3.7	3.1	−0.6	−16.3	14.3	16.4	2.1	14.7	11.6	8.3	−3.3	−28.6
3 (−5.6)	9.4	7.4	−2.0	−21.4	3.7	3.4	−0.3	−8.8	19.2	17.3	−1.9	−9.8	8.6	10.6	2.0	22.8
6 (−1.8)	11.2	9.5	−1.7	−15.7	4.7	4.3	−0.4	−7.4	14.5	16.2	1.7	11.6	7.0	6.7	−0.3	−3.7
9 (−6.3)	6.1	4.0	−2.1	−33.6	2.6	2.2	−0.4	−18.6	16.3	15.1	−1.2	−7.0	5.2	7.0	1.8	34.0
Mean ± s.d. (95% CI for differences)																
−4.4 ± 2.0* (−7.6, −1.2)	8.2 ± 2.6	6.8 ± 2.3	−1.4 ± 1.2 (−3.2, 0.6)	−15.8 ± 17.2 (−43.2, 11.5)	3.7 ± 0.8	3.2 ± 0.9	−0.4 ± 0.1‡ (−0.6, −0.2)	−12.8 ± 5.5 (−21.5, −4.0)	16.1 ± 2.3	16.3 ± 0.9	0.2 ± 2.0 (−3.0, 3.4)	2.4 ± 12.6 (−17.6, 22.4)	8.1 ± 2.7	8.2 ± 1.8	0.1 ± 2.4 (−3.9, 3.9)	6.1 ± 28.0 (−38.5, 50.7)
Group B																
1 (−30.9)	13.3	7.1	−6.2	−46.6	4.9	2.9	−2.0	−41.4	20.3	15.6	−4.7	−23.2	5.7	5.0	−0.7	−12.9
4 (−36.9)	13.3	5.6	−7.7	−57.9	5.2	1.8	−3.4	−65.4	18.0	12.4	−5.6	−30.9	6.6	7.4	0.8	11.8
5 (−24.9)	16.7	11.0	−5.7	−34.3	7.3	4.2	−3.1	−43.1	20.6	15.6	−5.0	−24.2	4.9	6.5	1.6	31.4
7 (−32.5)	17.0	9.7	−7.3	−43.0	7.2	3.4	−3.8	−53.4	16.8	11.6	−5.2	−30.9	5.0	6.4	1.4	27.2
8 (−23.0)	7.5	4.4	−3.1	−42.1	3.2	1.7	−1.5	−46.2	11.3	8.4	−2.9	−25.8	6.6	7.6	1.0	15.0
Mean ± s.d. (95% CI for differences)																
−29.6 ± 5.7* (−36.7, −22.6)	13.5 ± 3.8	7.5 ± 2.7	6.0 ± 1.8*‡ (−8.2, −3.8)	-44.8 ± 8.6 (−55.4, −34.1)	5.6 ± 1.7	2.8 ± 1.0	−2.8 ± 1.0*‡ (−4.0, −1.6)	−49.9 ± 9.8 (−62.1, −37.7)	17.4 ± 3.8	12.7 ± 3.0	−4.7 ± 1.0*‡ (−5.9, −3.4)	−27.0 ± 3.7 (−31.6, −22.4)	5.8 ± 0.8	6.6 ± 1.0	0.8 ± 0.9 (−0.3, 1.9)	14.5 ± 17.4 (−7.1, 36.1)

$CL_{1\text{-}MU}$, $CL_{3\text{-}MX}$, $CL_{1,3\text{-}DMU}$ are formation clearances (ml kg^{-1} h^{-1}) of 1-methyluric acid, 3-methylxanthine and 1,3-dimethyluric acid, respectively.
$CL_{R(Theophylline)}$ is the renal clearance (ml kg^{-1} h^{-1}) of theophylline.
T is the formation clearance of respective metabolite (or renal clearance of theophylline) after theophylline dose (day 1); T + C is clearance after ciprofloxacin treatment (day 5); and %Δ is percentage change in clearance values.
* $P \leq 0.01$ for comparison between groups A and B.
‡ $P < 0.01$ for within-group comparison between theophylline and theophylline + ciprofloxacin.

In group A there was a significant 13% decrease ($P < 0.01$) in the formation clearance of 3-MX after ciprofloxacin, while in group B formation clearances of 1-MU, 3-MX and 1,3-DMU were all decreased significantly ($P \leq 0.01$), by 45%, 50% and 27%, respectively. Changes in the renal clearance of theophylline, in the presence of ciprofloxacin, were highly variable but mean values were similar.

Total AUC of ciprofloxacin in group A subjects (11.8 ± 4.8 mg l^{-1} h) was not significantly different from that for group B (11.1 ± 4.5 mg l^{-1} h; $P > 0.05$).

Discussion

Four comprehensive studies of the pharmacokinetic interaction between ciprofloxacin and theophylline have been published [7–10], all of which reported a similar overall decrease in the clearance of theophylline. Wide inter-individual variability in the magnitude of the interaction was noted in two other studies [12, 13] but the reasons for such variability were not considered.

In the present study, the overall differences in theophylline pharmacokinetics were consistent with previous data, although of lower magnitude. Oral clearance was decreased by a mean of 19%, compared with 27–32% in previous studies and mean half-life was increased by 26% compared with 42–51% previously [7–10]. In agreement with the results of previous studies [8, 10, 23], the mean urinary recovery of theophylline and metabolites was high (85% in the control experiment and 75% during ciprofloxacin administration). The two phases of the study were not randomised, but were separated by a 4 day washout period.

The lower extent of inhibition of theophylline metabolism in our study relative to others might be attributable to decreased exposure to ciprofloxacin, a drug that is known to be a mixed competitive inhibitor of theophylline metabolism [4]. However, the mean AUC of ciprofloxacin was similar to that measured in other studies [24]. Alternatively, it is possible that wide inter-individual variation in the inhibitory potency of ciprofloxacin is the cause of the smaller effect on theophylline clearance. This is consistent with the observation that four of our subjects showed a mean decrease of only 4.4% in theophylline clearance, while in the remaining five, there was a mean 30% decrease (Figure 1a and b).

The small effect of ciprofloxacin in some subjects also might arise if ciprofloxacin differentially affected one or more of the metabolic pathways of theophylline. This possibility was evaluated by an analysis of the metabolite formation clearances in the two groups of subjects. In those subjects whose net theophylline clearance was relatively unaffected by ciprofloxacin (group A), the only significant change was a 13% decrease in 1-demethylation (to 3-MX). Three of the four subjects showed decreased 3-demethylation but this change did not achieve statistical significance ($P > 0.05$, statistical power = 0.69). The lack of change in 3-demethylation (to 1-MU) in our study should be interpreted cautiously as five subjects would be necessary for the statistical power to be greater than 0.8. In the subjects showing a mean 30% decrease in theophylline clearance (group B), 1-demethylation, 3-demethylation and 8-hydroxylation (to 1,3-DMU) were significantly decreased (by 50%, 45% and 27%, respectively). Previous studies [8, 10] have found decreases in the formation clearances of 3-MX (37–51%), 1-MU (42–47%) and 1,3-DMU (24–27%), with no significant change in the renal clearance of theophylline. Whilst the data from group B subjects are consistent with these results, our data indicate also that inter-individual variability in the potency of ciprofloxacin as an inhibitor of theophylline clearance arises from inter-individual differences in sensitivity to the inhibitory effects of ciprofloxacin. However, the significant inhibition of 8-hydroxylation in previous studies [8, 10], and in our group B subjects, is at variance with *in vitro* studies by Fuhr *et al.* [25] who found that quinolone antibiotics were at best weak inhibitors of the 8-hydroxylation of caffeine in human liver microsomes.

There are now several studies which indicate that different isoforms of cytochrome P450 are responsible for the 1- and 3-demethylation and the 8-hydroxylation pathways of metabolism of theophylline and the closely related methylxanthine caffeine [25–28]. K_m values for 1- and 3-demethylation of caffeine are similar, and substantially less than that for 8-hydroxylation [4, 8, 29]. Moreover, the 1- and 3-demethylations of caffeine correlate significantly with the CYP1A2 content of human liver microsomes. The 8-hydroxylation of caffeine is insensitive to inhibition by phenacetin (a selective inhibitor of CYP1A2), thus this pathway is not attributable to CYP1A2 [26]. Berthou *et al.* [26] also found that 3-demethylation was more sensitive to inhibition by phenacetin than 1-demethylation, which suggests that more than one enzyme may be involved. Finally, recent studies by Tassaneeyakul *et al.* [30] have shown that the 1-, 3- and 7-demethylations of caffeine in human liver microsomes are biphasic. The high affinity component was catalysed by cDNA expressed CYP1A2 and had similar K_m values to the expressed protein. The low affinity component for 1- and 7-demethylations correlated significantly with CYP2E1 activities and immunoreactive CYP2E1 content, and had K_m values similar to those for cDNA expressed CYP2E1. Correlation and inhibition data for 8-hydroxylation of caffeine were consistent with a major role for a CYP3A isoform.

Our data suggest that in individuals whose theophylline metabolism is sensitive to the effects of ciprofloxacin, inhibition of both CYP1A2 and CYP3A4 is important. In addition, the levels of CYP1A2 expression may be influential in understanding inter-individual variability in the inhibitory effects of ciprofloxacin. Ilett *et al.* [31] have recently shown that there is considerable inter-individual variability in the *in vivo* CYP1A2 metabolic activity towards caffeine, with a 28-fold range of values in normal, non-smoking subjects. Low levels of expression of CYP1A2 would be consistent with the lower

CL_m values for 1-MU and 3-MX and with the lesser degree of ciprofloxacin inhibition seen in group A compared with group B subjects. Alternatively, it is possible that variability in the effect of ciprofloxacin arises from inter-individual differences in K_i for ciprofloxacin.

If the k_a for theophylline (TheoDur®) is assumed to be 0.125 h^{-1} [32], then a 5 mg kg^{-1} dose given twice daily to our group A subjects would be predicted to produce mean steady-state trough and peak plasma drug concentrations of 9.3 and 11.5 mg l^{-1}, respectively, and 9.8 and 12.1 mg l^{-1}, respectively, during ciprofloxacin therapy. In group B subjects, the same dosage regimen would lead to steady-state trough and peak theophylline concentrations of 8.1 and 10.1 mg l^{-1}, rising to 12.4 and 14.4 mg l^{-1}, respectively, during treatment with ciprofloxacin. In one subject (No. 8), ciprofloxacin therapy should increase the peak serum theophylline concentration from 14.7 to 19.2 mg l^{-1}, thus increasing the risk of toxicity.

In summary, our study shows that the impact of the interaction between ciprofloxacin and theophylline varies considerably between different individuals. Following the addition of ciprofloxacin therapy, uniform decrease in theophylline dose would result in lower and possibly sub-therapeutic theophylline concentrations in a large proportion of the population whose theophylline metabolism is virtually unaffected by ciprofloxacin. Therefore, a suitable strategy for dealing with the interaction is to measure plasma theophylline concentration 2 to 3 days after the commencement of ciprofloxacin, and to decrease theophylline dosage only in those patients who exhibit a significant rise in theophylline concentration.

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