Br. J. clin. Pharmac. (1990), **29**, 491–493

Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline

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Nine healthy male volunteers were studied to assess the interaction between theophylline and ciprofloxacin and to assess whether a similar interaction occurred with lomefloxacin, using a randomised, crossover design. Subjects received theophylline 125 mg 8 hourly with and without lomefloxacin 400 mg 12 hourly or ciprofloxacin 500 mg 12 hourly for 7 days. Ciprofloxacin treatment lowered total theophylline clearance by 27%, owing to a decreased clearance via 1-, 3-demethylation and 8-hydroxylation. Lomefloxacin treatment did not alter theophylline clearance. Ciprofloxacin, at usual clinical doses, could cause a clinically significant interaction when co-administered with theophylline.

Keywords theophylline ciprofloxacin lomefloxacin interaction cytochrome P-450

Introduction

The fluoroquinolones are commonly used concurrently with theophylline for the treatment of infective bronchitis in patients with chronic obstructive airways disease. The ability of fluoroquinolones to inhibit theophylline clearance is well documented. The magnitude of the lowering in clearance varies between the fluoroquinolones with a 64% decrease in theophylline clearance by enoxacin (Rogge *et al.*, 1988; Wijnands *et al.*, 1986), and a 30% decrease with ciprofloxacin or pefloxacin (Bachmann *et al.*, 1988; Wijnands *et al.*, 1986). Theophylline is metabolised by three major pathways, 1-demethylation, 3-demethylation and 8-hydroxylation (Birkett *et al.*, 1985) and the effects of the fluoroquinolones on each of these metabolic pathways has not been established. This study was designed to identify which metabolic pathways are inhibited by ciprofloxacin and to test the hypothesis that lomefloxacin, a newer fluoroquinolone without a 4-oxo metabolite, does not inhibit theophylline metabolism.

Methods

The subjects were nine non-smoking male volunteers aged (mean ± s.d.) 23.3 ± 3.3 (range 19–29) years and weighing 76.5 ± 8.1 (range 66–89) kg who were healthy as determined by medical history, physical examination and standard biochemical and haematological parameters. Subjects abstained from methylxanthine-containing foods and beverages for 7 days prior to and during each study phase. No medications including alcohol, other than those required for the study, were taken for 1 week prior to and during each study phase. A randomised three way crossover study design was used with a 2 week washout period between each phase. The study details were explained fully to each subject who then gave written consent to participate. The studies were approved by the Christchurch Hospitals Ethics Committee.

Subjects received theophylline (Nuelin-Riker) 125 mg orally 8 hourly for 7 days in the control phase. In the ciprofloxacin phase, subjects received ciprofloxacin (Ciproxin-Bayer) 500 mg 12 hourly in addition to the theophylline for 7 days. In the lomefloxacin phase subjects received lomefloxacin (Searle) 400 mg orally 12 hourly in addition to the theophylline for 7 days. The doses of ciprofloxacin and lomefloxacin used were based on the dosage recommended by their respective manufacturer. On day 7 of each phase venous blood samples (5 ml) were collected through an indwelling intravenous catheter prior to and at 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h

after the morning dose. On each study day the ciprofloxacin or lomefloxacin was administered at the same time as the theophylline. Total urine was collected over the same 8 h dosing interval in each phase. Plasma was separated and stored at −20° C until analysed and urine was diluted 1:1 with 0.1 M acetic acid and kept at −20° C until analysed.

Analytical procedures

Plasma theophylline concentrations were measured by high performance liquid chromatography (Birkett *et al.*, 1985). The concentrations of theophylline and theophylline metabolites (3-methylxanthine [3MX], 1-methyluric acid [1MU], and 1,3-dimethyluric acid [1,3DMU] in urine were measured using high performance liquid chromatography (Birkett *et al.*, 1985). Pure theophylline and pure theophylline metabolites were obtained commercially: theophylline from Hamilton Laboratories, Adelaide, Australia; DMU and 3MX from Fluka A G, Switzerland; IMU from Adams Chemical Company, Illinois, U.S.A. In all assays the intra-assay coefficients of variation were less than 7%.

Analysis of results

The area under the plasma theophylline concentration-time curve over the dose interval (AUC) was calculated using the linear trapezoidal rule and oral theophylline clearance (CL_o) as:

$$CL_o = \text{Dose}/(\text{AUC} \times \text{BW})$$

where BW is body weight in kg. Partial metabolic and renal clearances of theophylline were calculated as:

$$CL_i = f_i \times CL$$

where CL_i is the metabolic clearance to 1MU (CL_{1MU}), 3MX (CL_{3MX}) or 1,3DMU (CL_{DMU}) or the renal clearance of unchanged theophylline (CL_R), and f_i is the fractional urinary recovery of each metabolite as a fraction of the total recovery of theophylline and its metabolites. This method of calculating partial metabolic clearances assumes that 100% of the theophylline dose is recovered as parent drug and measured metabolites.

Results are expressed as mean ± s.d. The significance of the differences between study phases was determined by repeated measures analysis of variance and subsequent pair comparisons were performed using Student's paired *t*-test.

Results

The effects of pretreatment with ciprofloxacin and lomefloxacin on theophylline oral clearance (CL_o) and on the renal and metabolic clearances of theophylline are summarised in Table 1.

Ciprofloxacin reduced theophylline CL_o by (mean difference ± s.d. difference) 0.220 ± 0.075 ml min^{-1} kg^{-1} ($P < 0.05$). The reduction in CL_o was the result of a mean decrease in CL_{DMU} of 0.082 ± 0.031 ml min^{-1} kg^{-1} ($P < 0.05$); a reduction in CL_{1MU} of 0.104 ± 0.021 ml min^{-1} kg^{-1} ($P < 0.05$) and a reduction in CL_{3MX} of 0.052 ± 0.018 ml min^{-1} kg^{-1} ($P < 0.05$). Renal clearance of unchanged theophylline was not significantly altered by ciprofloxacin pretreatment.

Lomefloxacin did not significantly alter the total plasma clearance of theophylline or the renal and metabolic clearances of theophylline and its metabolites.

The recoveries of theophylline derived urinary products were not statistically different in each phase, being (mean ± s.e. mean) 102 ± 9%, 88 ± 11% and 94 ± 11% in the control, ciprofloxacin and lomefloxacin phases, respectively. The attainment of steady-state on the 3 study days was confirmed by trough concentrations within 10% at the beginning and the end of each dosage interval. The study design was sufficiently sensitive to detect a 6–8% change in the measured parameters for theophylline with an α value of 0.05 and a β value of 0.2.

Discussion

Ciprofloxacin treatment lowered mean plasma theophylline clearance by 27%, consistent with the 30% reduction in theophylline clearance reported previously (Wijnands *et al.*, 1986; Bachmann *et al.*, 1988). Clearance by all three metabolic pathways was lowered, although the decrease via the 8-hydroxylation pathway (24%) was less than the decrease via the 1-demethylation (37%) and 3-demethylation (42%) pathways. The difference in the lowering of clearance via 8-hydroxylation was not statistically different ($P > 0.05$) from those in clearance via 1-demethylation and 3-demethylation. However, the inhibitory effect of ciprofloxacin pretreatment on the disposition of theophylline was consistent with previously published *in vitro* data (Robson *et al.*, 1987, 1988b) and *in vivo* data (Robson *et al.*, 1988a) suggesting that two isozymes of cytochrome P450 are involved in the metabolism of theophylline, one isozyme predominantly

performing the demethylations and the other performing the 8-hydroxylation.

Lomefloxacin treatment had no effect on theophylline metabolism consistent with the hypothesis that it is the 4-oxo metabolites of the fluoroquinolones which inhibit theophylline metabolism (Wijnands *et al.*, 1986). Lomefloxacin, unlike ciprofloxacin, does not form a 4-oxo metabolite.

Our data suggest that the reduction in theophylline clearance by ciprofloxacin is of clinical importance because of the low therapeutic index of theophylline and a dosage reduction of theophylline is required when these drugs are co-administered. In contrast, lomefloxacin and theophylline can be safely co-administered.

Elizabeth Murdoch kindly typed the manuscript. The authors gratefully acknowledge the assistance of Staff Nurse A. M. McGinlay and financial support from Searle Pharmaceuticals, Australia.

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(Received 29 June 1989, accepted 28 November 1989)

Table 1 Effect of ciprofloxacin and lomefloxacin on the metabolic and renal clearance of theophylline

	CL_o*			CL_{1MU}			CL_{3MX}			CL_{DMU}			CL_R		
Subject	*T*	*TC*	*TL*	*T*	*TC*	*TL*	*T*	*TC*	*TL*	*T*	*TC*	*TL*	*T*	*TC*	*TL*
1	0.546	0.662	0.634	0.197	0.182	0.291	0.079	0.132	0.075	0.228	0.256	0.223	0.043	0.092	0.045
2	0.797	0.632	0.889	0.242	0.164	0.397	0.103	0.069	0.149	0.374	0.303	0.205	0.078	0.097	0.087
3	0.551	0.388	0.506	0.164	0.106	0.147	0.127	0.060	0.124	0.223	0.167	0.198	0.038	0.055	0.037
4	0.898	0.693	1.060	0.329	0.150	0.362	0.161	0.103	0.192	0.369	0.340	0.426	0.039	0.099	0.081
5	1.034	0.662	1.032	0.340	0.173	0.333	0.186	0.097	0.174	0.443	0.307	0.424	0.065	0.085	0.100
6	0.549	0.501	0.618	0.173	0.084	0.159	0.086	0.075	0.111	0.232	0.208	0.284	0.058	0.134	0.064
7	0.725	0.483	0.781	0.216	0.117	0.217	0.152	0.062	0.144	0.310	0.260	0.352	0.048	0.044	0.068
8	1.719	1.017	1.151	0.432	0.228	0.349	0.285	0.147	0.221	0.712	0.411	0.464	0.291	0.232	0.117
9	0.613	0.415	0.628	0.151	0.102	0.156	0.083	0.052	0.084	0.297	0.198	0.313	0.083	0.062	0.074
Mean	0.826	0.606	0.811	0.249	0.145	0.268	0.140	0.089	0.142	0.354	0.272	0.321	0.083	0.100	0.075
s.d.	0.376	0.192	0.231	0.097	0.047	0.099	0.066	0.034	0.049	0.154	0.077	0.102	0.080	0.056	0.025
P		0.02	NS		0.01	NS		0.02	NS		0.03	NS		NS	NS

*Units of clearance of ml min^{-1} kg^{-1}
T, Theophylline alone; TL, Theophylline plus lomefloxacin; TC, Theophylline plus ciprofloxacin