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Effect of Norfloxacin on Theophylline Pharmacokinetics at Steady State

SUSAN K. BOWLES,[1,2] ZAGORKA POPOVSKI,[1] MICHAEL J. RYBAK,[1,2] HOWARD B. BECKMAN,[3,4] AND DAVID J. EDWARDS[1,2]*

College of Pharmacy and Allied Health Professions[1] and School of Medicine,[3] Wayne State University, Detroit, Michigan 48202, and Departments of Pharmacy Services[2] and Medicine,[4] Detroit Receiving Hospital/University Health Center, Detroit, Michigan 48201

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Norfloxacin is a currently marketed fluoroquinolone antibiotic. Other quinolones which are structurally similar to norfloxacin, particularly enoxacin, inhibit theophylline clearance. Since norfloxacin may be administered to patients also receiving theophylline, we studied the effect of norfloxacin on the pharmacokinetics of theophylline in 10 healthy male volunteers. A randomized, crossover study design with a 2-week washout period between treatments was used. Subjects received oral theophylline (200 mg of aminophylline [theophylline ethylenediamine]) three times daily for 4 days either alone or with 400 mg of norfloxacin (orally) twice daily for the same period. Theophylline concentrations in serum were significantly higher ($P < 0.05$) at 0, 3, 4, 10, and 12 h following the final dose in the norfloxacin treatment group than in the group receiving only theophylline. However, mean theophylline oral clearance was not significantly different between the two treatments (2.85 ± 0.68 liters/h without norfloxacin versus 2.56 ± 0.53 liters/h with norfloxacin [$P = 0.08$]). Similarly, no significant differences were observed in theophylline half-life ($P = 0.11$). We conclude that norfloxacin is unlikely to have a clinically significant effect on theophylline disposition in most patients.

Norfloxacin is a currently marketed member of a new class of antibiotics known as the fluoroquinolones. The addition of 6-fluoro and 7-piperazino substituents to the basic structure of nalidixic acid has resulted in a series of agents that are effective against a wide range of microorganisms. Quinolone antibiotics other than norfloxacin include amifloxacin, ciprofloxacin, enoxacin, ofloxacin, and pefloxacin (10).

While clinical experience has demonstrated that these drugs are relatively free of serious side effects, several of the quinolone compounds have been found to inhibit the clearance of theophylline. Enoxacin appears to be the most potent inhibitor of this class (8, 9), with ciprofloxacin and pefloxacin also causing a decrease in theophylline clearance which may be of clinical significance (4, 6, 9). Studies with ofloxacin have generally reported small changes in theophylline clearance (1, 7, 9).

It is clear that the fluoroquinolone antibiotics have the potential to produce clinically significant alterations in theophylline clearance, although the magnitude of the effect varies widely among compounds. Given the structural similarities between norfloxacin and other members of this class, it is reasonable to suggest that norfloxacin may also affect theophylline pharmacokinetics. To date only one study examining the effect of norfloxacin on theophylline disposition has been reported, and no significant changes were observed (7). However, this study was conducted with only five volunteers, who received a norfloxacin dosage lower than that commonly used. The purpose of our investigation was to determine the effect of a typical multiple-dosing regimen of norfloxacin on the pharmacokinetics of theophylline at steady state.

* Corresponding author.

MATERIALS AND METHODS

Subjects. Ten healthy male volunteers ranging in age from 24 to 34 years were recruited for this study. All subjects underwent a complete medical history and physical exam which included a 12-lead electrocardiogram, blood count, serum chemistry, and urinalysis. The volunteers were nonsmokers with no history of substance abuse, and all were within 20% of ideal body weight. Each subject abstained from alcohol and xanthine-containing substances beginning 48 h prior to the start of the study and continued to do so throughout the study. This study was approved by the Human Investigation Committee at Wayne State University, and written informed consent was obtained from each volunteer.

Study design. A randomized, cross-over study design with a 2-week washout period between phases was used. Subjects received 200 mg of aminophylline (theophylline ethylenediamine; Searle and Co., San Juan, P.R.) orally three times daily (at 8 a.m., 4 p.m., and 12 p.m.) for 3 days and a single 200-mg dose on the morning of day 4 (at 8 a.m.). Aminophylline was administered alone or with 400 mg of norfloxacin (Merck Sharp & Dohme, West Point, Pa.) orally twice daily (at 8 a.m. and 8 p.m.) for 3 days and as a single 400-mg dose on the morning of day 4 (at 8 a.m.). No food was permitted for 8 h prior to the final dose of aminophylline or for 4 h afterward. Blood was drawn from each subject prior to the 8 a.m. dose of aminophylline on each study day and at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 h following the final dose. Serum was collected and stored at −20°C prior to analysis.

Theophylline assay. Theophylline concentrations in serum were determined by a fluorescence polarization method (TDx; Abbott Diagnostics, Irving, Tex.). The mean between-day coefficients of variation for controls were 7.3, 5.9, and 4.7% at 3.5, 7.0, and 12.0 μg/ml, respectively. Within-day variabilities averaged 5.7, 3.7, and 4.2% at 3.5, 7.0, and 12.0 μg/ml, respectively. Norfloxacin did not interfere with

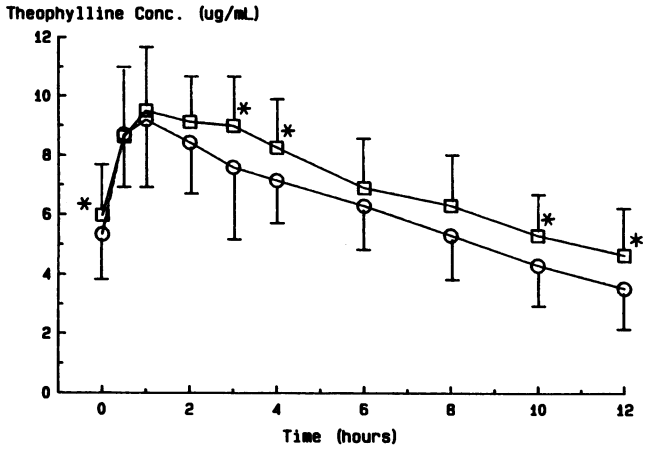

FIG. 1. Concentrations in serum of theophylline following administration of 200 mg of aminophylline three times daily for 10 doses either alone (○) or with 400 mg of norfloxacin twice daily (□). An asterisk (*) indicates statistical significance ($P < 0.05$).

the analytical procedure. All samples were assayed within 2 weeks of collection.

Datum analysis. Pharmacokinetic parameters for theophylline following the final dose were calculated by noncompartmental methods. The area under the serum concentration-time curve from 0 to 8 h was determined by the LaGrange method (5). Theophylline oral clearance was calculated by dividing the administered dose (200 mg of aminophylline; equivalent to 158 mg of theophylline) by the area under the serum concentration-time curve from 0 to 8 h. The elimination rate constant (k_{el}) and half-life of theophylline were obtained by linear regression analysis of the terminal phase of the concentration-time profile.

Statistics. Pharmacokinetic parameters between treatment groups were compared by analysis of variance for a two-level cross-over design. A value of $P < 0.05$ was considered significant in all cases.

RESULTS

Significantly higher ($P < 0.05$) theophylline concentrations in serum were found prior to the 8 a.m. dose on day 3 (5.98 versus 4.92 μg/ml) and day 4 (5.97 versus 5.33 μg/ml) in norfloxacin-treated subjects. Theophylline concentration immediately prior to the final dose was not significantly different from the value 8 h following the dose (5.33 versus 5.30 μg/ml in subjects receiving theophylline alone; 5.97 versus 6.31 μg/ml in norfloxacin-treated subjects) in either treatment group, indicating that steady-state conditions had been achieved with both treatments. Concentrations were significantly higher 3.0, 4.0, 10.0, and 12.0 h after the final dose of theophylline in the norfloxacin-treated group (Fig. 1). Table 1 summarizes the pharmacokinetic data obtained. Coadministration of norfloxacin increased the area under the theophylline concentration-time curve from 0 to 8 h by 10.5% from a value of 57.89 ± 11.63 to 63.95 ± 12.41 ($P = 0.07$), while mean oral clearance decreased 11.3% from a control value of 2.85 ± 0.68 to 2.56 ± 0.56 liters/h with norfloxacin treatment ($P = 0.08$). Eight subjects experienced a decrease and two subjects experienced an increase in clearance following norfloxacin administration, with changes ranging from an increase of 22.5% to a decrease of 28.3%. No significant differences were observed in the elimination rate constant ($P = 0.09$) or half-life ($P = 0.11$) between the treatments. The incidence of minor side effects such as nausea (in 5 of 10 subjects) and insomnia (in 3 of 10 subjects) was the same with both treatments. One subject receiving theophylline alone and two subjects receiving both drugs in combination experienced diarrhea during drug treatment.

DISCUSSION

Studies reporting the effect of fluoroquinolones on theophylline pharmacokinetics indicate that these compounds inhibit theophylline metabolism to a variable extent. Enoxacin appears to be the most potent inhibitor. Wijnands et al. (8) reported that theophylline concentrations in serum rose from a mean value of 8.5 μg/ml before administration of enoxacin to 21.7 μg/ml during coadministration of enoxacin to 14 patients. In a subsequent study, total body clearance of theophylline was reduced by 63.6% by enoxacin (9). Studies with ciprofloxacin have produced somewhat inconsistent results. Wijnands et al. (9) reported a 30.4% decrease in mean theophylline clearance following 500 mg of ciprofloxacin administered twice daily. Raoof et al. (4) found that theophylline concentrations increased by an average of 87% in patients receiving 750 mg of ciprofloxacin twice daily.

TABLE 1. Pharmacokinetic parameters of theophylline administered alone or with norfloxacin[a]

Subject	AUC_{0-8}		CL_o (liters per h)		k_{el} (h^{-1})		$t_{1/2}$ (h)	
	A	B	A	B	A	B	A	B
1	52.52	61.32	3.01	2.58	0.144	0.046	4.81	15.02
2	72.27	85.74	2.19	1.84	0.073	0.077	9.46	9.01
3	46.59	65.11	3.39	2.43	0.096	0.078	7.24	8.95
4	69.12	80.14	2.29	1.97	0.099	0.068	6.96	10.19
5	35.60	42.19	4.44	3.74	0.146	0.118	4.75	5.86
6	56.89	62.89	2.78	2.51	0.113	0.073	6.14	9.55
7	57.59	69.74	2.74	2.27	0.056	0.051	12.27	13.70
8	72.77	59.50	2.17	2.66	0.066	0.075	10.54	9.29
9	56.10	56.41	2.82	2.80	0.104	0.107	6.63	6.49
10	59.48	56.49	2.66	2.80	0.072	0.064	9.65	10.88
Mean ± SD[b]	57.89 ± 11.62	63.95 ± 12.41	2.85 ± 0.68	2.56 ± 0.53	0.097 ± 0.031	0.076 ± 0.22	7.84 ± 2.52	9.89 ± 2.83

[a] Abbreviations: AUC_{0-8}, area under the serum concentration-time curve from 0 to 8 h; CL_o, oral clearance; k_{el}, elimination rate constant; $t_{1/2}$, half life; A, aminophylline alone; B, aminophylline plus norfloxacin.

[b] Probability values were as follows: area under the serum concentration-time curve from 0 to 8 h, $P = 0.07$; oral clearance, $P = 0.08$; elimination rate constant, $P = 0.09$; half-life, $P = 0.11$.

Using a similar dosage of ciprofloxacin, Nix et al. (2) observed no significant changes in mean theophylline clearance after 7 days of ciprofloxacin pretreatment. However, a potentially important interaction was noted in three subjects whose theophylline clearances decreased by 42 to 113%. Ofloxacin appears to be a relatively weak inhibitor with 5.1% (9), 12.1% (1), and 0% (7) decreases in theophylline clearance reported.

In general, changes in theophylline clearance of less than 20% are unlikely to be of clinical significance. In this study, the administration of norfloxacin at a dosage of 800 mg/day resulted in an average decrease in the oral clearance of theophylline of 11.3%, a value which approached ($P = 0.08$) but did not reach statistical significance. Although theophylline concentrations were significantly elevated during administration of norfloxacin at several time points following the final dose (Fig. 1), the largest increase during the final dosing interval was only 18.4% at 3.0 h. Sano et al. (7) reported a decrease in theophylline clearance averaging 7.4% in five healthy volunteers receiving 600 mg of norfloxacin per day. The results of our study should be applicable to patients receiving norfloxacin, since 400 mg twice daily is the usual dosage for treatment of most infections and steady-state conditions would be expected after administration for 3 days, given the usual half-life for norfloxacin of 3 to 7 h. In addition, the theophylline concentrations observed here were at steady state and were close to the usual therapeutic range (peak concentrations of 9.2 and 9.5 μg/ml for control and norfloxacin-treated groups, respectively). More inhibition of theophylline clearance would not be expected at higher theophylline concentrations if fluoroquinolones inhibit metabolism by a competitive mechanism.

The reason for the apparent small effect of norfloxacin on theophylline pharmacokinetics is unclear. It has been suggested that inhibition of metabolism by these compounds is related to the production of the 4-oxoquinolone metabolite. However, this hypothesis has not yet been confirmed. Wijnands et al. (9) observed a significant correlation between the percentage of the dose excreted as 4-oxoquinolone and the degree of inhibition of metabolism produced by enoxacin, ciprofloxacin, and pefloxacin. In the case of norfloxacin, the oxoquinolone metabolite is the major product recovered in urine, but it has not been detected in serum following doses as large as 1,600 mg (3). Structural differences between these drugs may also be important. Enoxacin has a naphthyrindine ring with nitrogen atoms at positions 1 and 8. Norfloxacin, like ciprofloxacin, ofloxacin, and pefloxacin, lacks the nitrogen at position 8. However, nalidixic acid, which retains this nitrogen, has been shown to have no effect on theophylline clearance (8).

From the results of this study we conclude that norfloxacin does not have a clinically significant effect on theophylline pharmacokinetics and should be relatively safe for use in patients who are also receiving theophylline. However, it is possible that under conditions different from those of this study, larger and potentially clinically significant effects could occur in some patient populations. Data for ciprofloxacin suggest that a greater degree of inhibition of theophylline clearance occurs in elderly patients (4, 6). Therefore, we recommend that patients receiving norfloxacin and theophylline concomitantly be monitored carefully for signs of theophylline toxicity and, preferably, with frequent theophylline concentration measurements.

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