ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1989, p. 212–214
0066-4804/89/020212-03$02.00/0

Vol. 33, No. 2

Effect of Norfloxacin on Theophylline Metabolism

ROBIN L. DAVIS,[1]* H. WILLIAM KELLY,[1,2] RONALD W. QUENZER,[3] JIM STANDEFER,[4] BRENDA STEINBERG,[1] AND JOHN GALLEGOS[1]

College of Pharmacy[1] and Departments of Pediatrics[2] and Pathology[4] and Division of Infectious Diseases,[3] School of Medicine, University of New Mexico, Albuquerque, New Mexico 87131

Received 2 May 1988/Accepted 15 November 1988

The purpose of this study was to investigate the effect of norfloxacin on theophylline elimination. Ten normal volunteers were studied. In a randomized crossover sequence, each subject received 6 mg of aminophylline per kg of body weight by a 30-min intravenous infusion on day 4 of taking norfloxacin (400 mg every 12 h) or while drug free. Mean theophylline clearance decreased and mean elimination half-life increased after norfloxacin administration (from 0.036 ± 0.006 to 0.033 ± 0.004 liter/h per kg and from 8.7 ± 1.2 to 9.5 ± 1.5 h, respectively; $P < 0.05$, Wilcoxon signed-ranks test). We conclude that norfloxacin taken in recommended doses for 3 days has a small inhibitory effect on theophylline metabolism that would probably not cause clinically important elevations in theophylline concentrations in most patients.

Norfloxacin is a new quinolone antimicrobial agent recently approved for clinical use by the Food and Drug Administration. Coadministration of theophylline with three structurally related compounds, enoxacin, pefloxacin, and ciprofloxacin, has been reported to increase theophylline concentrations and cause toxicity (2, 8, 11, 13–16); coadministration with nalidixic acid, another quinolone, does not (16). Ofloxacin has been reported to decrease or have no effect on theophylline clearance (3, 5, 16). It has been postulated that the 4-oxoquinolone metabolites rather than the parent drug cause the drug interaction (6, 16). Norfloxacin is metabolized to such a compound (17). We therefore sought to determine the effect of norfloxacin on theophylline pharmacokinetics.

The purposes of this study were to (i) investigate the effect of norfloxacin on theophylline clearance and (ii) determine if any specific metabolic pathway is affected.

MATERIALS AND METHODS

Study population. Ten healthy, nonsmoking adults (four females and six males, ages 22 to 38) participated in the study, which was approved by the Human Research Review Committee at our institution. All subjects had normal results for physical examinations, urinalysis, and hematologic and biochemical studies. All subjects were within 10% of their ideal body weight (range, 54 to 89 kg).

Drug administration. In a randomized, crossover sequence, subjects were administered 6 mg of aminophylline per kg of body weight by intravenous infusion over 30 min on day 4 of taking norfloxacin (400 mg every 12 h) or while drug free. The study periods were separated by 1 week. Subjects abstained from alcohol, foods known to induce drug metabolism, and other drugs for at least 72 h prior to receiving any study drug. Subjects also abstained from caffeine for at least 48 h prior to receiving aminophylline.

Sample collection. Blood was taken from an indwelling cannula immediately before and 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the aminophylline infusion. The blood was allowed to clot at room temperature, the samples were centrifuged at 800 × *g*, and the serum was collected. Urine was collected 0 to 24 h after aminophylline administration.

Serum assays. Serum samples were analyzed for theophylline concentrations by a previously described high-performance liquid chromatographic method with β-hydroxyethyl theophylline as an internal standard (7). The interday coefficient of variation for spiked serum standards was 5% for 10 μg/ml and 5.6% for 2.5 μg/ml.

Urine assays. Urine samples were analyzed for theophylline and theophylline metabolites by high-performance liquid chromatography as follows. For extraction, 0.2 ml of urine was mixed with 1.0 ml of 0.01 M sodium acetate, pH 4.0, containing β-hydroxyethyl theophylline as an internal standard. This mixture was applied to a solid-phase extraction column (LC-18; Supelco, Inc.) that had been washed twice with 1 ml of methanol and 1 ml of sodium acetate. The adsorbed drugs were washed with 1 ml of sodium acetate and eluted with two 0.5-ml washes of methanol. The methanol was evaporated, and the residue was reconstituted with 0.2 ml of sodium acetate. Recovery was 90% for all drugs except 3-methyluric acid and 1-methyluric acid, for which recovery averaged 40%.

For separation, the reconstituted residue was injected onto a 3-μm APEX II octadecyl column (250 by 4.6 mm; Jones Chromatography). The mobile phase consisted of a gradient mixture of two solutions: solution A, containing 0.2% tetrahydrofuran in 0.01 M sodium acetate (pH 4.0), and solution B, containing 0.01 M sodium acetate (pH 4.0), methanol, and tetrahydrofuran at a ratio of 73.5:25:1.5, respectively. A linear gradient was initiated with 100% solution A–0% solution B, changing to 15% A–85% B at 25 min. Five minutes was allowed for reequilibration. The column was maintained at 50°C, the flow rate was 0.8 ml/min, and the effluent was monitored at 273 nm. The detection limit was 1 μg/ml, with an upper limit of linearity of 100 μg/ml. The between-run coefficients of variation for theophylline, 1,3-dimethyluric acid, 1-methyluric acid, and 3-methylxanthine were 2.5, 9.2, 6.1, and 8.9%, respectively, at 10 μg/ml and 4.1, 5.4, 8.9, and 5.1%, respectively, at 50 μg/ml.

Pharmacokinetic analysis. Data were analyzed by model-independent pharmacokinetic methods (4). The area under the curve (AUC) of theophylline concentration versus time from zero hours to infinity ($AUC_{0-\infty}$) and the area under the first moment of the concentration-time curve (AUMC) for each treatment were calculated by the trapezoidal rule. Total

* Corresponding author.

TABLE 1. Theophylline pharmacokinetic parameters[a] with and without norfloxacin coadministration

Group	C_{max} (μg/ml)	CL (liter/h per kg)	CL_{renal} (liter/h per kg)	MRT (h)	$t_{1/2}$ (h)	k_{el} (h^{-1})	V_{ss} (liter/kg)
Control	10.6 ± 1.3	0.036 ± 0.006	0.006 ± 0.002	12.4 ± 1.7	8.7 ± 1.2	0.081 ± 0.11	0.44 ± 0.05
Norfloxacin	11.1 ± 1.4	0.033 ± 0.004	0.007 ± 0.002	13.6 ± 2.1	9.5 ± 1.5	0.074 ± 0.11	0.44 ± 0.07
P	0.26	0.047	0.37	0.075	0.047	0.059	0.88

[a] Mean ± standard deviation. Abbreviations: C_{max}, maximum concentration in serum; CL, clearance; CL_{renal}, renal clearance; MRT, mean residence time; $t_{1/2}$, elimination half-life; k_{el}, elimination rate constant; V_{ss}, steady-state volume of distribution.

body clearance of theophylline was calculated from the theophylline dose divided by the $AUC_{0-\infty}$. The mean residence time for theophylline was calculated from the AUMC divided by the AUC. The steady-state apparent volume of distribution was calculated as $D(AUMC_{0-\infty}/AUC_{0-\infty}^2) - (TD/2AUC_{0-\infty})$, where D is theophylline dose and T is duration of infusion (10). The terminal elimination rate constant was estimated from the slope of a least-squares linear regression of the linear portion of the curve of the logarithm of the concentration versus time. The elimination half-life was calculated as 0.693 divided by the terminal elimination rate constant. Theophylline renal clearance was calculated as the amount of parent drug excreted in the urine in 24 h divided by the AUC during that period (4).

Statistical analysis. Differences in theophylline parameters with and without norfloxacin coadministration were analyzed for statistical significance by both parametric (paired Student's *t* test) and nonparametric (Wilcoxon rank-sum test) means (18).

RESULTS

Mean data for theophylline pharmacokinetic parameters with and without norfloxacin coadministration are listed in Table 1. The maximum concentration of aminophylline in serum was similar in both phases of the study. Theophylline clearance decreased in 9 of 10 subjects and elimination half-life increased in 8 of 10 subjects given norfloxacin. These changes were statistically significant ($P = 0.047$ for both). The theophylline steady-state apparent volume of distribution and renal clearance were not influenced by norfloxacin.

Urine was collected and analyzed for the concentration of theophylline and its metabolites in nine subjects. The fractions of theophylline recovered as parent drug and its three major metabolites (3-methylxanthine, 1,3-dimethyluric acid, and 1-methyluric acid) are shown in Fig. 1. Mean recovery of the parent drug was slightly higher and mean recovery of the metabolites was slightly lower after norfloxacin administration; the difference was statistically significant only for 1-methyluric acid ($P = 0.02$).

DISCUSSION

The quinolone carboxylic acids enoxacin, perfloxacin, and ciprofloxacin have been reported to decrease theophylline clearance (2, 8, 11, 13–16), while nalidixic acid does not (16). Ofloxacin has been reported to decrease or to have no effect on theophylline clearance (3, 5, 16).

Other investigations into the effect of norfloxacin on theophylline clearance have yielded conflicting results. Nor-

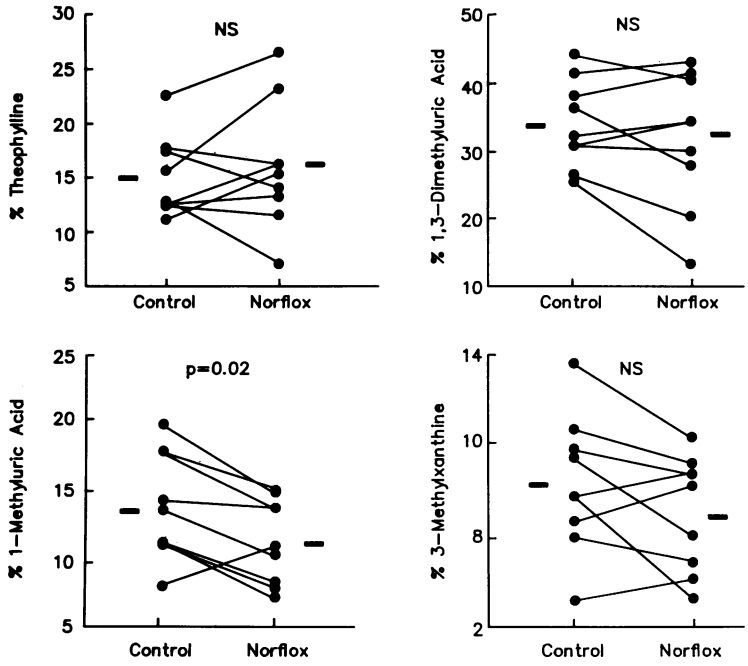

FIG. 1. Fractions of theophylline and its major metabolites recovered in the urine of nine subjects 0 to 24 h after they received aminophylline with or without norfloxacin coadministration. NS, Not significant ($P > 0.05$).

floxacin decreased theophylline clearance in two studies that were similar to ours, but the results did not reach statistical significance. In a study by Sano et al. (12), five subjects were given 250 mg of intravenous aminophylline while drug free or on day 4 of taking norfloxacin (200 mg three times daily). Mean theophylline clearance decreased 8.0% and elimination rate constant decreased 14.9% after norfloxacin administration. Bowles et al. (1) reported a mean decrease in steady-state theophylline clearance of 10.2% in 10 subjects on day 4 of taking norfloxacin (400 mg twice daily).

Niki et al. (9) reported a 10% increase in the AUC of theophylline concentration versus time and a statistically significant increase in the maximum concentration of theophylline in serum in five subjects on day 3 of taking norfloxacin (200 mg three times daily); however, data for these parameters approached control values on day 5 of norfloxacin coadministration. In contrast, Tierney and Dales (Clin. Pharmacol. Ther. **43**:156, 1988) reported a larger, statistically significant decrease in theophylline clearance (14.9%; $P < 0.01$) and an increase in elimination half-life (15.7%; $P < 0.02$), with no significant change in steady-state volume of distribution. The reasons for the larger effects seen in that study are unclear. Tierney and Dales studied eight subjects given a 5-mg/kg dose of aminophylline while otherwise drug free or after 6 days of norfloxacin (400 mg twice daily). It is possible that longer periods of norfloxacin administration allow its 4-oxoquinolone metabolite to accumulate and produce a greater inhibitory effect on hepatic metabolism. An investigation comparing the effects of short and long periods of norfloxacin administration on hepatic enzyme activity with measurement of 4-oxoquinolone is needed to resolve this issue.

We measured the urinary recovery of theophylline and its metabolites to determine which metabolic pathways were inhibited by norfloxacin. Metabolism to 1-3-dimethyluric acid, 3-methylxanthine, and the intermediate, 1-methylxanthine, is catalyzed by hepatic cytochrome P-450 (6). 1-Methylxanthine is rapidly converted by xanthine oxidase to 1-methyluric acid (6). Changes in metabolic pathways after norfloxacin administration were statistically significant and consistently lower only for 1-methyluric acid formation. It is possible that the decrease in 1-methyluric acid formation was due to inhibition of xanthine oxidase. Since endogenous uric acid formation is dependent on xanthine oxidase, we measured serum uric acid concentrations in five of our subjects before and after norfloxacin administration. Uric acid concentrations increased in three and decreased in two subjects, indicating that norfloxacin has no effect on xanthine oxidase.

In conclusion, administration of norfloxacin to our subjects for 4 days resulted in a small but statistically significant decrease in mean theophylline clearance and an increase in elimination half-life. This small inhibition of theophylline metabolism would probably not result in clinically important elevations in steady-state theophylline concentrations or decreased dosing requirements in most patients. For example, a constant aminophylline infusion of 0.7 mg/kg per h would yield an average steady-state theophylline concentration of 16.5 μg/ml in our subjects, which would rise to 18.2-μg/ml norfloxacin coadministration. In the subject with the maximal observed decrease in clearance (26.6%), steady-state theophylline concentrations would increase from 12.6 to 17.2 μg/ml. Because of the intersubject variability in inhibition, it would be prudent to monitor theophylline concentrations during norfloxacin coadministration in patients exhibiting signs of theophylline toxicity or in those who have theophylline concentrations near the upper limit of the therapeutic range.

ACKNOWLEDGMENT

This work was supported in part by Public Health Service grant NIH 5 MO1 RR00997-12 from the General Clinical Research Program, DRR.

LITERATURE CITED

1. **Bowles, S. K., Z. Popovski, M. J. Ryback, H. B. Beckman, and D. J. Edwards.** 1988. Effect of norfloxacin on theophylline pharmacokinetics at steady state. Antimicrob. Agents Chemother. **32**:510–512.
2. **Davies, B. I., F. P. Maesen, and J. P. Teengs.** 1984. Serum and sputum concentrations of enoxacin after oral dosing in a clinical and bacteriological study. J. Antimicrob. Chemother. **14**(Suppl. C):83–89.
3. **Fourtillan, J. B., J. Granier, B. Saint-Salv, J. Salmon, A. Surjus, D. Tremblay, M. V. Du Laurier, and S. Beck.** 1986. Pharmacokinetics of ofloxacin and theophylline alone and in combination. Infection **14**:S67–S69.
4. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed. Marcel Dekker, Inc., New York.
5. **Gregoire, S. L., T. H. Grasela, Jr., J. P. Freer, K. J. Tack, and J. J. Schentag.** 1987. Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. Antimicrob. Agents Chemother. **31**:375–378.
6. **Hendeles, L., M. Massanari, and M. Weinberger.** 1986. Theophylline, p. 1105–1188. *In* W. E. Evans, J. S. Schentag, and W. A. Jusko (ed.), Applied pharmacokinetics: principles of therapeutic drug monitoring, 2nd ed. Applied Therapeutics, Inc., Spokane, Wash.
7. **Kelly, H. W., J. R. Powell, and J. F. Donohue.** 1986. Ranitidine at very large doses does not inhibit theophylline elimination. Clin. Pharmacol. Ther. **39**:577–581.
8. **Maesen, F. I. V., J. P. Teengs, C. Baur, and B. I. Davies.** 1984. Quinolones and raised plasma concentrations of theophylline. Lancet **ii**:530.
9. **Niki, Y., R. Soejima, H. Kawane, M. Sumi, and S. Uneki.** 1987. New synthetic quinolone antibacterial agents and serum concentrations of theophylline. Chest **92**:663–669.
10. **Perrier, D., and M. Mayersohn.** 1982. Noncompartmental determination of the steady-state volume of distribution for any mode of administration. J. Pharm. Sci. **71**:372–373.
11. **Raoof, S., C. Wollschlager, and H. Khan.** 1987. Ciprofloxacin increases serum levels of theophylline. Am. J. Med. **82**(Suppl. 4A):115–118.
12. **Sano, M., I. Yamanoto, J. Ueda, H. Yoshashina, and M. Goto.** 1987. Comparative pharmacokinetics of theophylline following two fluoroquinolones co-administration. Eur. J. Clin. Pharmacol. **32**:431–432.
13. **Wijnands, W. J. A., A. J. A. van Griethuysen, T. B. Vree, B. van Klingeren, and C. L. A. van Herwaarden.** 1986. Enoxacin in lower respiratory tract infections. J. Antimicrob. Chemother. **18**:719–727.
14. **Wijnands, W. J. A., C. L. A. van Herwaarden, and T. B. Vree.** 1984. Enoxacin raises plasma theophylline concentrations. Lancet **ii**:108–109.
15. **Wijnands, W. J. A., T. B. Vree, and C. L. A. van Herwaarden.** 1985. Enoxacin decreases the clearance of theophylline in man. Br. J. Clin. Pharmacol. **20**:583–588.
16. **Wijnands, W. J. A., T. B. Vree, and C. L. A. van Herwaarden.** 1986. The influence of quinolone derivatives on theophylline clearance. Br. J. Clin. Pharmacol. **22**:677–683.
17. **Wise, R.** 1984. Norfloxacin—a review of pharmacology and tissue penetration. J. Antimicrob. Chemother. **13**(Suppl. B): 59–64.
18. **Zar, J. H.** 1984. Biostatistical analysis, 2nd ed. Prentice-Hall, Inc., Englewood Cliffs, N.J.