

Effects of Enoxacin on Renal and Metabolic Clearance of Theophylline in Rats

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The effects of enoxacin and its metabolite 4-oxoenoxacin on the disposition of theophylline were investigated in rats. Systemic clearance of theophylline was significantly decreased by approximately 40, 46, and 50% after oral coadministration of 25, 100, and 200 mg of enoxacin per kg, respectively. No significant changes in the volume of distribution of theophylline were observed. 4-Oxoenoxacin had no direct effect on theophylline disposition. Significant changes in urinary excretion of theophylline and its metabolites were observed. (i) Urinary excretion of unchanged theophylline was significantly increased in proportion to increases in enoxacin dosage. (ii) Decreases in renal clearance of theophylline and metabolic clearance of 1-methyluric acid and 1,3-dimethyluric acid were observed. (iii) The percent decreases in the metabolic clearance of 1-methyluric acid were dependent on enoxacin dosage. It is likely that enoxacin inhibits the elimination process, which depends on cytochrome P-450-mediated isozymes for N demethylation and oxidation, and that the capacity of the inhibitory effect of enoxacin is greater in the N-demethylation pathway than it is in oxidation.

A number of new oral quinolone antimicrobial agents, including enoxacin, have been developed recently. These agents have strong activity against both gram-positive and gram-negative bacteria. Some quinolone antimicrobial agents, however, are known to cause clinically important problems when they are coadministered with theophylline; this is because of the narrow therapeutic range of theophylline and because quinolones induce increases in the concentration of theophylline in plasma, which increases the risk of side effects (4, 6, 13, 15-17, 19). The first report on the pharmacokinetic interaction between a quinolone, enoxacin, and theophylline was presented by Wijnands et al. (17), who indicated that the theophylline concentration in plasma is significantly elevated after coadministration of enoxacin and theophylline in patients with reversible airway diseases. Therefore, the interaction of enoxacin with theophylline was examined in this study.

The mechanism of interaction of enoxacin with theophylline has generally been considered to be inhibition of theophylline metabolism since theophylline is extensively metabolized by the hepatic mixed-function oxidase system, such as those of cytochrome P-450 and its isomers. The main pathways for theophylline metabolism have been accepted to be N-1 or N-3 demethylation and C-8 oxidation in humans (2, 7, 13) and rats (10, 20). However, there is no information relating to the effect of enoxacin on the two differential metabolic pathways of theophylline in rats.

In the present study, the inhibitory effect of enoxacin on the disposition of theophylline was investigated in rats. The interaction of theophylline with a metabolite of enoxacin, 4-oxoenoxacin, which is thought to be the main cause of this interaction (19), was also examined.

MATERIALS AND METHODS

Chemicals. Theophylline was obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). 1-Methyluric acid (1MU), 1-methylxanthine, and 1,3-dimethyluric acid (DMU) were purchased from Sigma Chemical Co. (St. Louis, Mo.). Enoxacin and its metabolite 4-oxoenoxacin were kindly supplied by Dainippon Pharmaceutical Co. (Osaka, Japan). Lomefloxacin (NY-198), which was used as an internal standard for determining the enoxacin concentration in plasma, was obtained from Hokuriku Seiyaku Co., Ltd. (Fukui, Japan). All other chemicals were commercially available and were of analytical grade.

Animals and treatments. Male Wistar rats (age, 7 to 9 weeks; weight, 300 to 350 g; Shizuoka Laboratory Animal Center, Shizuoka, Japan) were used in this study. Theophylline and 4-oxoenoxacin were suspended in isotonic saline solution, and sodium hydroxide (1 N) was added in drops to create a clear solution. Enoxacin was suspended with 0.5% carboxymethyl cellulose. Urinary excretion and systemic clearance experiments were carried out in a crossover fashion with washout periods of 1 week. Rats were fasted for 16 h before each experiment.

In the first experiment, testing for urinary excretion, theophylline (10 mg/kg) was administered intravenously into the left jugular vein, which was exposed under light ether anesthesia. Enoxacin was administered orally to the enoxacin pretreatment groups at 25, 100, or 200 mg/kg 1 h before the administration of theophylline. After theophylline administration, rats were housed in metabolic cages and urine was collected for 48 h.

One day before the experiments for determination of systemic clearance, rats were anesthetized with sodium pentobarbital (40 mg/kg) and cannulated in the right jugular vein with polyethylene tubing. Theophylline and enoxacin were administered as described above for the urinary excretion experiments, except that the cannula was used as the route for theophylline administration. 4-Oxoenoxacin (20 mg/kg) was administered intravenously 10 min before the

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administration of theophylline. Blood samples of 0.25 ml each were collected at intervals of 5, 15, 30, 45, 60, 90, 120, 180, 240, and 300 min; and plasma was obtained by centrifugation at $6,000 \times g$ for 5 min. All plasma and urine samples were stored at -40°C until they were analyzed.

Analytical procedure. Concentrations of theophylline in plasma and urine were determined by high-performance liquid chromatography with a UV spectrophotometric detector (LC-4A and LC-6A systems, respectively; Shimadzu, Kyoto, Japan). The concentration of theophylline in plasma was determined as described previously (12). For analysis of theophylline, 1MU, 1-methylxanthine, and DMU in urine, portions of diluted urine samples were passed through a filter (pore size, $0.45 \mu\text{m}$; Nihon Millipore Kogyo, Yonezawa, Japan) and were injected directly onto the high-performance liquid chromatography column. Conditions and parameters were as follows: column, Cosmosil 5C₁₈ (4.6 by 150 mm; Nacalai Tesque Inc., Kyoto, Japan); mobile phase, phosphoric acid-potassium dihydrogen phosphate solution (pH 2.5) and methanol (96/4; by volume); flow rate, 1.0 ml/min; wavelength, 278 nm; column temperature, 35°C . For the calculations, standard curves for all compounds were measured over a range of 1 to 12 $\mu\text{g/ml}$ and were shown to be linear. Compound recovery ranged from 95 to 101%, with the coefficient of variation being less than 5%. Blank urine samples did not interfere with the peak corresponding to each compound.

Enoxacin concentrations in plasma were measured by high-performance liquid chromatography on a chromatograph equipped with a fluorescence detector (LC-6A system and RF 535; Shimadzu). A total of 350 μl of acetonitrile containing NY-198 (0.3 $\mu\text{g/ml}$) as an internal standard was added to 50 μl of a plasma sample and vortexed. After centrifugation, 300 μl of the supernatant was evaporated to dryness under a gentle stream of nitrogen at 40°C . The residue that was obtained was dissolved in the mobile phase (200 μl) and then injected onto the chromatograph. Conditions and parameters for enoxacin determination were as follows: column, Cosmosil 5C₁₈ (4.6 by 150 mm); mobile phase, 0.05 M citric acid, 1 M ammonium acetate, and acetonitrile (84/1/15; by volume); flow rate, 1.2 ml/min; wavelengths for excitation and emission, 330 and 400 nm, respectively; column temperature, 40°C . The assay was shown to be linear for the concentrations that we studied. The coefficients of variation for the assay were less than 6%.

Data analysis. The plasma concentration-time data for theophylline in the control group and in each group of rats pretreated with enoxacin were analyzed on the basis of noncompartmental analysis. The area under the curve (AUC) was calculated by the trapezoidal rule method with extrapolation to infinity. Systemic clearance (CL) was determined as $\text{CL} = \text{dose}/\text{AUC}$. The mean residence time (MRT) was calculated as $\text{MRT} = \text{AUMC}/\text{AUC}$, with AUMC representing the area under the first moment curve. Partial metabolic clearance and renal clearance of theophylline were calculated as $\text{CL}_M = f_M \times \text{CL}$, where f_M represents the recovery of each metabolite or unchanged theophylline in urine as a fraction of total excretion.

Statistical analysis. Results are expressed as means \pm standard errors. Statistical differences between the control and the enoxacin pretreatment groups were examined by analysis of variance, and the Tukey test was used to detect the difference among individual groups. Statistical significance was defined as $P < 0.05$.

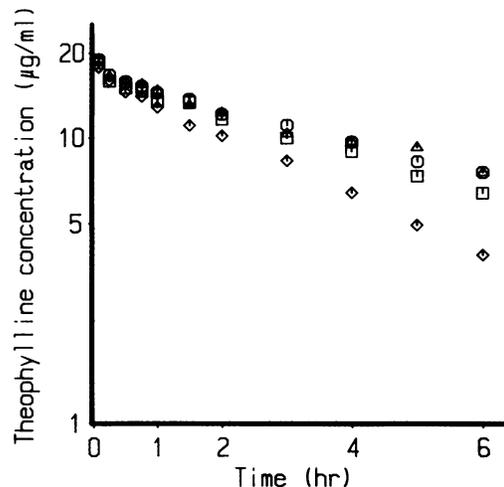


FIG. 1. Semilogarithmic plots of plasma concentration-time data for theophylline in control (\diamond) and enoxacin-treated (\square , 25 mg/kg; \triangle , 100 mg; \triangle , 200 mg/kg) rats after administration of a single intravenous dose of theophylline (10 mg/kg). Each point represents the mean.

RESULTS

Mean plasma concentration-time curves of theophylline in control and enoxacin-treated rats are shown in Fig. 1. Enoxacin increased the theophylline level in plasma and delayed the disappearance of theophylline from plasma. Because the concentration-time data of theophylline for some rats were most suitable for the monoexponential equation, and because the biexponential equation was used for the remaining rats, the corresponding pharmacokinetic parameters of theophylline were estimated by model-independent methods. The pharmacokinetics of the interaction between theophylline and enoxacin are given in Table 1. Systemic clearance of theophylline in enoxacin-treated rats decreased significantly as the dosage of enoxacin was increased. Mean residence time had the same tendency, with significant reductions observed in the enoxacin-treated group (analysis of variance). However, no significant difference in the steady-state volume of distribution was observed between the control and enoxacin-treated groups. In contrast, concentrations of theophylline in plasma in the 4-oxo-enoxacin-treated group showed no significant change (Fig. 2), and 4-oxo-enoxacin did not have any effect on the pharmacokinetic parameters of theophylline (Table 1). Figure 3 is a semilogarithmic plot of the plasma concentration-time data of enoxacin for rats that were pretreated with 25 and 100 mg of enoxacin per kg.

Table 2 lists the urinary excretion of theophylline and its metabolites during the urine collection period (48 h). Total urinary recovery was 94.60 to 105.50% of the dosage, with no differences being noted between the groups. A significant reduction of 1MU excretion was observed in enoxacin-treated rats. A statistical difference in 1MU excretion was found between the groups that were given dosages of 100 and 200 mg of enoxacin per kg; however, only a slight decrease in DMU was found. In contrast, the urinary excretion of unchanged theophylline was significantly increased in proportion to the enoxacin dosage increases.

The effects of enoxacin on the renal clearance of theophylline and the metabolic clearance to 1MU and DMU are given in Table 3. Renal clearance of theophylline in the enoxacin-

TABLE 1. Effect of enoxacin on the pharmacokinetics of theophylline^a

Treatment	No. of rats	CL (ml/h per kg)	MRT (h)	V _{ss} (liter/kg)
Control	5	143.92 ± 2.80	4.194 ± 0.206	0.601 ± 0.018
Enoxacin				
25 mg/kg	4	87.11 ± 6.21 ^b	8.088 ± 1.438	0.686 ± 0.089
100 mg/kg	4	77.88 ± 4.88 ^b	8.106 ± 1.087	0.616 ± 0.040
200 mg/kg	5	72.28 ± 4.08 ^b	9.474 ± 0.716 ^b	0.674 ± 0.013
4-Oxoenoaxacin	4	141.37 ± 10.16	4.225 ± 0.219	0.591 ± 0.021

^a Values are means ± standard errors. Abbreviations: CL, clearance; MRT, mean residence time; V_{ss}, volume of distribution at steady state.

^b Values are significantly different from those for the control ($P < 0.05$).

treated groups was significantly decreased, by approximately 20% from that of the control, yet no significant difference was observed between each treatment group. Metabolic clearance in enoxacin-treated rats was also significantly decreased compared with that in control rats. A decrease in DMU formation clearance was observed in rats given a dosage of 25 mg of enoxacin per kg, which was the same degree as the decrease in 1MU formation clearance; however, no remarkable reduction was found when the enoxacin dosage was increased from 25 to 200 mg/kg.

DISCUSSION

In the present study, coadministration of enoxacin in dosages ranging from 25 to 200 mg/kg was shown to elevate the concentration of theophylline in plasma and to delay the disappearance of theophylline from the bodies of both rats and humans (Fig. 1). The pharmacokinetic parameters also indicated that enoxacin has a potent inhibitory effect on theophylline clearance. The dose of enoxacin administered to rats in this study was selected so that the therapeutic concentrations observed in humans could be achieved. The concentrations of enoxacin in plasma were measured after administration of dosages of 25 and 100 mg/kg, and peak levels were about 1.2 and 2.4 µg/ml, respectively. In experiments on the interaction between enoxacin and theophylline,

in humans, Rogge et al. (13) demonstrated that the mean peak concentrations of enoxacin in plasma after oral administration of dosages of 25, 100, and 400 mg every 12 h were recorded as 0.153, 0.640, and 1.94 µg/ml, respectively. The decrease in theophylline clearance observed in this study (40 to 50%) reflects the results of that study (66 to 73%) with similar concentration ranges of enoxacin, since the contribution of metabolites to theophylline clearance is probably smaller in rats than it is in humans. Therefore, rats are useful for predicting the possible interaction of theophylline with quinolones in humans.

The effect of enoxacin on theophylline clearance appeared to be dose dependent, and no differences are found in the volume of distribution. Nakamura et al. (11) have reported that enoxacin possesses weak protein-binding characteristics; the unbound fraction with serum protein was about 0.66. In addition, Wijnands et al. (18) have suggested that enoxacin does not change the binding of theophylline to plasma protein in humans. No change in the volume of distribution observed in this study supports the lack of an effect of enoxacin on the protein binding of theophylline. The cause of the decrease in the theophylline clearance induced by enoxacin, therefore, may be due to inhibition of theophylline metabolism.

Results of several studies with Sprague-Dawley rats have suggested that theophylline metabolism is carried out only by the two pathways: N-3 demethylation following oxidation

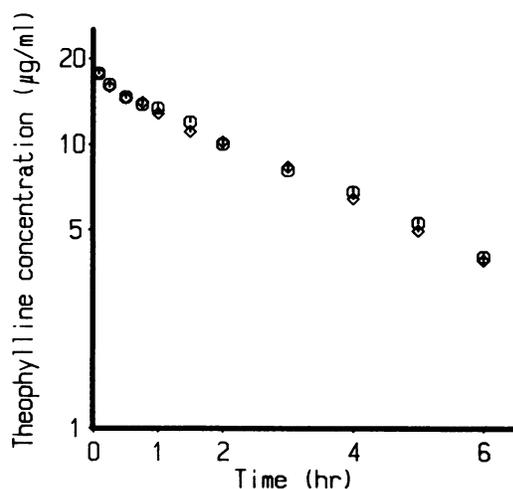


FIG. 2. Semilogarithmic plots of plasma concentration-time data for theophylline in control (◇) and 4-oxoenoaxacin-treated (○, 20 mg/kg) rats after administration of a single intravenous dose of theophylline (10 mg/kg). Each point represents the mean.

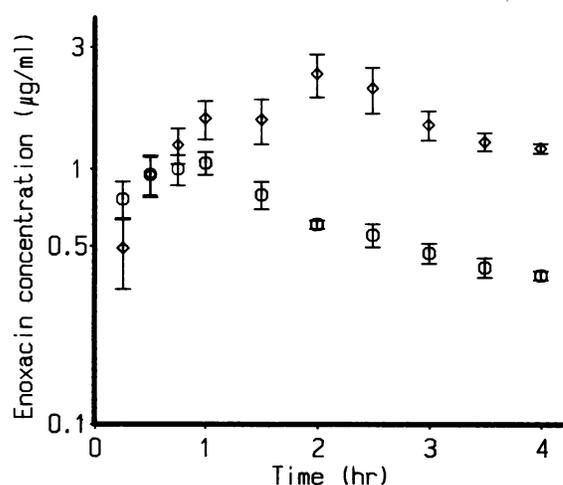


FIG. 3. Semilogarithmic plots of plasma concentration-time data for enoxacin in rats after administration of a single oral dose of enoxacin (□, 25 mg/kg; ◇, 100 mg/kg). Each point represents the mean ± standard error ($n = 4$).

TABLE 2. Effect of enoxacin on urinary excretion of theophylline and its metabolites^a

Treatment	% Total recovery in urine		
	Metabolite		Theophylline
	1MU	DMU	
Control	34.37 ± 1.11	29.34 ± 0.92	36.55 ± 1.91
Enoxacin			
25 mg/kg	30.82 ± 1.37	26.09 ± 0.76	43.04 ± 1.97
100 mg/kg	24.02 ± 0.18 ^{b,c}	24.49 ± 0.35	52.02 ± 0.58 ^b
200 mg/kg	21.27 ± 0.51 ^{b,c}	25.60 ± 1.10	53.12 ± 1.59 ^{b,c}

^a Values are means ± standard errors.

^b Values are significantly different from those for the control ($P < 0.05$).

^c Values are significantly different from those for enoxacin at 25 mg/kg ($P < 0.05$).

and C-8 oxidation for 1MU and DMU (10, 20). In addition, the fraction of excretion of metabolites into urine is lower in rats than it is in humans: about 50% of the theophylline dosage is excreted in an unchanged form. The metabolites observed in this study with the Wistar strain of rats were also 1MU and DMU, although the percent excretion was not equal to that found in Sprague-Dawley rats. In fact, 3-methylxanthine could not be detected, and total urinary recovery was approximately 100% of the dosage administered.

Pretreatment of rats with enoxacin decreased the percent urinary excretion of theophylline metabolites, while it increased the percent urinary excretion of unchanged theophylline, indicating that theophylline metabolism is inhibited by enoxacin in rats to the same extent as it is in humans. However, renal clearance of theophylline in enoxacin-treated rats was decreased by 20% compared with that in control rats (Table 3). Wijnands et al. (19) have reported that enoxacin has no effect on the renal clearance of theophylline in humans. In contrast, Sano et al. (14) have suggested that some quinolones, including enoxacin, have an inhibitory effect on the renal excretion of theophylline. Beckmann et al. (1) also showed that enoxacin reduces the renal clearance of 1MU, 3-methylxanthine, and DMU by inhibiting tubular secretion and that there is a decrease in the renal clearance of theophylline without any significant differences. The results of the present study support those findings. Based on these observations, a decrease in renal clearance induced by enoxacin is most likely caused by an inhibitory effect on the tubular secretion of theophylline.

A number of reports have suggested that the most important mechanism for reducing theophylline clearance is the

TABLE 3. Effect of enoxacin on renal clearance of theophylline and partial clearance to each metabolite^a

Treatment	Metabolic clearance (ml/h per kg) of:		Renal clearance (ml/h per kg) of theophylline
	1MU	DMU	
Control	49.403 ± 1.397	42.181 ± 1.260	50.694 ± 3.027
Enoxacin			
25 mg/kg	26.887 ± 2.429 ^b	22.821 ± 2.156 ^b	37.359 ± 2.443
100 mg/kg	18.697 ± 1.134 ^b	19.086 ± 1.297 ^b	40.539 ± 2.729
200 mg/kg	15.342 ± 0.810 ^{b,c}	18.485 ± 1.221 ^b	38.444 ± 2.714

^a Values are means ± standard errors.

^b Values are significantly different from those for the control ($P < 0.05$).

^c Values are significantly different from those for enoxacin at 25 mg/kg ($P < 0.05$).

inhibitory effect of enoxacin on theophylline metabolism. A significant decrease in the metabolic clearance of both 1MU and DMU suggests that enoxacin affects the metabolism of theophylline for 1MU and DMU formation in rats (Table 3). However, some reports have demonstrated that N demethylation and C-8 oxidation are carried out by different forms of cytochrome P-450 in humans. Grygiel et al. (7) have shown that a differential inhibitory effect of cimetidine on theophylline metabolic pathways is selective and that the two demethylation reactions, N-1 and N-3 demethylation, are a common form of cytochrome P-450 distinct from the reaction involved in C-8 oxidation, in which cimetidine inhibits only N demethylation. Similar observations in experiments of paraxanthine metabolism were reported by Lelo et al. (9). Some studies with rats, on the other hand, have also demonstrated that theophylline metabolism involves two different isozymes of cytochrome P-450 (3, 20). Results of the present study indicate that enoxacin decreases the metabolic pathways of 1MU and DMU to the same extent, indicating that enoxacin inhibits two different isozymes of cytochrome P-450 and that enoxacin has no effect on xanthine oxidase since 1-methylxanthine could not be detected. In addition, Edwards et al. (5) have reported that pretreatment of rats with enoxacin induces a large decrease in the clearance of antipyrine, which is metabolized by at least three different isozymes of cytochrome P-450 (8). On the basis of these findings, we propose that enoxacin competitively inhibits a wide variety of metabolic reactions of cytochrome P-450 and interacts with many other drugs. Moreover, the dose-dependent inhibitory effect of enoxacin on theophylline metabolism observed in this study was stronger for the metabolic clearance of 1MU than for that of DMU (Table 3); the metabolic clearance of 1MU was decreased by 54, 38, and 31% of the control value for enoxacin doses of 25, 100, and 200 mg/kg, respectively, with no decrease in DMU being observed between enoxacin treatments of 100 and 200 mg/kg. Therefore, it may be concluded that the capacity of the inhibitory effect of enoxacin on theophylline metabolism is large in the N-demethylation pathway.

Wijnands et al. (19) have proposed that the mechanism of pharmacokinetic and metabolic interactions between enoxacin and theophylline is caused by the 4-oxo metabolite of quinolones. However, our previous studies in humans demonstrated that a newly developed quinolone, T-3262, which does not form the 4-oxo metabolite, has a moderate inhibitory effect (30%) on theophylline clearance (15). In their basic experimental study with rats, Edwards et al. (5) showed that enoxacin had a significant effect on the disposition of antipyrine, whereas its metabolite 4-oxoenoxacin was not a key factor. We investigated whether the 4-oxo metabolite plays an important role in the mechanism of inhibition of theophylline metabolism; results of the present study show that 4-oxoenoxacin has no effect on the disposition of theophylline, which supports the findings of Edwards et al. (5). These observations suggest that the 4-oxo metabolite of enoxacin does not have a direct influence on theophylline disposition and that the main cause of this interaction may depend on the enoxacin molecule.

The results of the present study demonstrate that enoxacin affects renal excretion and at least two different metabolic pathways of theophylline in rats as well as humans. The capacity for this inhibitory effect of enoxacin seems to be larger in the N-demethylation pathway than in the C-8-oxidation pathway, although the percent decrease in both pathways was similar at enoxacin dosages of 25 mg/kg. On

the basis of these observations, further studies are needed to examine the possibility that enoxacin interacts with other drugs which are metabolized by mixed-function oxidase systems.

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