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# The Possible Mechanism of Interaction between Xanthines and Quinolone

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**Abstract**—To clarify the mechanism of interaction between theophylline and enoxacin, the effects of enoxacin and its metabolite, 4-oxo-enoxacin, on the disposition of new xanthine derivatives, 1-methyl-3-propylxanthine (MPX) and 3-propylxanthine (enprofylline), as models of theophylline have been investigated in rats. Pretreatment with enoxacin significantly delayed the elimination of MPX from plasma. No significant change in the volume of distribution of MPX was observed in the presence of enoxacin, but the total body clearance of MPX was significantly decreased by approximately 60 and 80% after pretreatment with 25 and 100 mg $kg^{-1}$ of enoxacin, respectively. The amount of the decrease in total body clearance depended on the dose of enoxacin. 4-Oxo-enoxacin had little or no effect on MPX disposition. A newly developed quinolone, NY-198, which does not affect the disposition of theophylline, also did not affect the disposition of MPX. Enoxacin also had no effect on the disposition of enprofylline. These results indicate that the mechanism for decrease in theophylline clearance induced by enoxacin may not be due to its metabolite, 4-oxo-enoxacin, but to enoxacin itself, and that enoxacin does not inhibit solely the elimination process depending on cytochrome P450 isoenzyme for *N*-demethylation. It is likely that enoxacin has no influence on the renal excretion of xanthines.

Xanthine derivatives, including theophylline, have been found to be useful in the treatment of bronchial asthma. However, new quinolone antibacterial drugs are preferred for treating respiratory disease infections because of their strong antimicrobial activity against Gram-positive and Gram-negative bacteria. But when coadministered with theophylline, some quinolone antibacterial drugs may cause clinical problems because of an induced decrease in theophylline clearance which increases the risk of serious side effects developing (Wijnands et al 1984; Gregoire et al 1987; Raoof et al 1987; George et al 1988). In particular, the interaction between theophylline and enoxacin has been extensively discussed (Wijnands et al 1986; Beckmann et al 1987; Edwards et al 1988; Harder et al 1988; Takagi et al 1988b; Carbo et al 1989).

The mechanism of decrease in theophylline clearance induced by quinolones has generally been considered to be an inhibition of theophylline metabolism: quinolones are capable of competitively inhibiting cytochrome P450 activity in hepatic microsomes and theophylline is metabolized by the cytochrome P450 system. The quinolone metabolite, 4-oxo-quinolone, seems to be the main cause of the change in theophylline metabolic clearance due to competitive inhibition of the *N*-demethylation pathway of theophylline (Wijnands et al 1986).

Our previous studies have shown that in man the interaction between theophylline and quinolones is not solely dependent on the 4-oxo metabolite (Takagi et al 1988b). The magnitude of this interaction, however, and the affected metabolic pathways have not been adequately elucidated. The present study was carried out using the new xanthine derivatives, 1-methyl-3-propylxanthine (MPX) and 3-propylxanthine (enprofylline), as models of theophylline, to investigate how quinolones change theophylline disposition in rats. The chemical structures of both xanthines are similar to those of theophylline, but there are differences in the biotransformation of MPX (Apichartpichean et al 1988) and enprofylline (Persson et al 1982).

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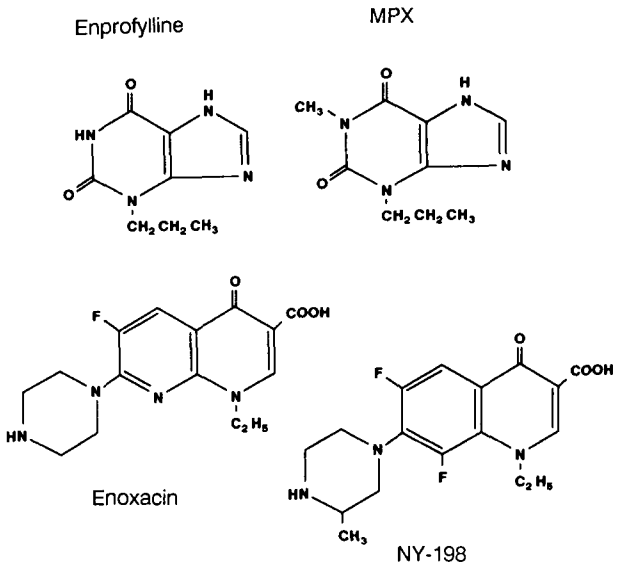
## Materials and Methods

*Chemicals*

The *N*-alkyl-substituted xanthine derivatives, 1-methyl-3-propylxanthine (MPX), 1-methyl-3-butylxanthine (MBX), 3-propylxanthine (enprofylline) and 3-butylxanthine (BX), (I) were synthesized in our laboratories (Apichartpichean et al 1988; Takagi et al 1988a). Enoxacin and its metabolite, 4-oxo-enoxacin, were kindly supplied by Dainippon Pharmaceutical Co. Ltd, Osaka, Japan. NY-198 ((±)-1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride) was obtained from Hokuriku Seiyaku Co. Ltd, Fukui, Japan. All other chemicals were commercially available and of analytical grade. MPX, enprofylline and 4-oxo-enoxacin were suspended in 0·9% NaCl (saline) and sodium hydroxide (2 M) was added in drops to create a clear solution. Enoxacin and NY-198 were suspended with 0·5% carboxymethylcellulose.

*Procedures*

Nine-week-old male Wistar strain rats (Shizuoka Laboratory Animal Center, Shizuoka, Japan), 280–300 g, were used. Food and water were freely available. One day before experimentation, rats were anaesthetized with sodium pentobarbitone (40 mg $kg^{-1}$) and cannulated with polyethylene tubing in the right jugular vein, then allowed to recover. After overnight fasting but with free access to water, rats were divided into four treatment groups: (1) control group




I. Chemical structures of 1-methyl-3-propylxanthine (MPX), 3-propylxanthine (enprofylline), enoxacin and NY-198.

(MPX and enprofylline were administered intravenously at 2·5 mg $kg^{-1}$); (2) enoxacin pretreated group (enoxacin was administered orally at 25 or 100 mg $kg^{-1}$ 1 h before administration of MPX or enprofylline); (3) 4-oxo-enoxacin pretreated group (4-oxo-enoxacin was administered intravenously at 5 or 20 mg $kg^{-1}$ 10 min before administration of MPX); (4) NY-198 pretreated group (NY-198 was administered orally at 25 mg $kg^{-1}$ 1 h before administration of MPX). Blood samples of about 0·3 mL each were collected at 10, 20 30, 45, 60 and 90 min for enprofylline and thereafter 120, 150 and 180 min for MPX. Plasma samples were obtained by centrifugation at 6000 *g* for 5 min and stored at −40°C until analysis.

*Drug analysis*

The HPLC apparatus was a Shimadzu LC-6A system (Shimadzu Co., Kyoto, Japan) consisting of an LC-6A liquid pump, an SPD-6AV UV-VIS spectrophotometric detector and SIL-6A autoinjector. The column was a Cosmosil $5C_{18}$ column (Nacalai Tesque, Kyoto, Japan). The mobile phases were 30 mM $KH_2PO_4$ (pH 5·0)–methanol (80:20; v/v) and 30 mM $KH_2PO_4$ (pH 3·0)–methanol (60:40; v/v) for enprofylline and MPX, respectively. 4-Oxo-enoxacin and MPX concentrations were simultaneously determined. The mobile phase was employed at a flow rate of 1·5 and 1·0 mL $min^{-1}$ for enprofylline and MPX, respectively. The elutions were carried out at 50 and 35°C, respectively, and the effluent column was monitored at 274 nm.

In a 1·5 mL plastic centrifuge tube, 50 μL of plasma and 0·2 mL of the internal standard solution (MBX 0·5 μg $mL^{-1}$ and BX 0·5 μg $mL^{-1}$ in methanol for MPX and enprofylline, respectively) were vortexed and centrifuged at 6000 *g* for 2 min. Supernatant (0·2 mL) was added to a glass culture tube and evaporated to dryness in a gentle stream of nitrogen at 40°C. The residue was reconstituted with 0·2 mL of the mobile phase and 150 μL was injected into the column. MPX, enprofylline and 4-oxo-enoxacin were measured over the linear range of 0·05 to 12 μg $mL^{-1}$; the detection limit for each drug was 0·05 μg $mL^{-1}$.

*Protein binding*

The study of the effect of enoxacin on plasma protein binding of MPX was carried out by ultrafiltration at room temperature (25°C), using a commercially available MPS-1 device (Amicon Corp., MA, USA). The binding of MPX was determined at a concentration of 10 μg $mL^{-1}$ both in the absence and in the presence of enoxacin of varying concentrations (0·1–0·5 μg $mL^{-1}$) in fresh plasma obtained from rats (n = 3). Free MPX concentration was determined by measuring MPX in the ultrafiltrate. A preliminary experiment, using MPX concentration of 10 μg $mL^{-1}$ in isotonic phosphate-buffered saline (pH 7·4) and MPX in the ultrafiltrate, showed adsorption of MPX to the device was negligible.

*Data analysis*

Concentration-time data of each drug were analysed on the basis of a one-compartment open model using the non-linear least-squares method program, MULTI, written by Yamaoka et al (1981). The area under the curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity. Total body clearance (CL) was determined by CL = Dose/AUC. The area under the first moment curve (AUMC) was calculated from time zero to the last sample time with extrapolation to time infinity using the least-squares terminal slope (Benet & Galeazzi 1979). The mean residence time (MRT) was calculated by MRT = AUMC/AUC.

*Statistical analysis*

Results were expressed as mean ± standard error. Statistical analysis was assessed by one-way analysis of variance. Statistical significance was defined as $P < 0.05$ using Tukey's multiple comparison procedure (Tukey 1949).

## Results

Semilogarithmic data of plasma disappearance of MPX after a single intravenous administration at a dose of 2·5 mg $kg^{-1}$ with and without enoxacin (25 and 100 mg $kg^{-1}$) or NY-198 (25 mg $kg^{-1}$) are shown in Fig. 1. Plasma disappearance of MPX declined monoexponentially in both control and treated rats. Plasma concentrations of MPX during the elimination phase were significantly increased by enoxacin treatment. On the other hand, NY-198 did not alter plasma concentrations of MPX. Pharmacokinetic parameters of MPX are shown in Table 1. When data obtained from the separate experiments were analysed independently and statistically, significant decreases in the elimination rate constant ($K_{el}$) and total body clearance (CL) were observed between the control group and the enoxacin-pretreated groups: the elimination rate constant for MPX after pretreatment with enoxacin was significantly reduced by 65 and 83% for 25 and 100 mg $kg^{-1}$ doses of enoxacin, respectively, compared with the control group. Pretreatment with enoxacin significantly reduced the total body clearance of MPX by 63 and 81% for 25 and 100 mg $kg^{-1}$ doses of enoxacin,

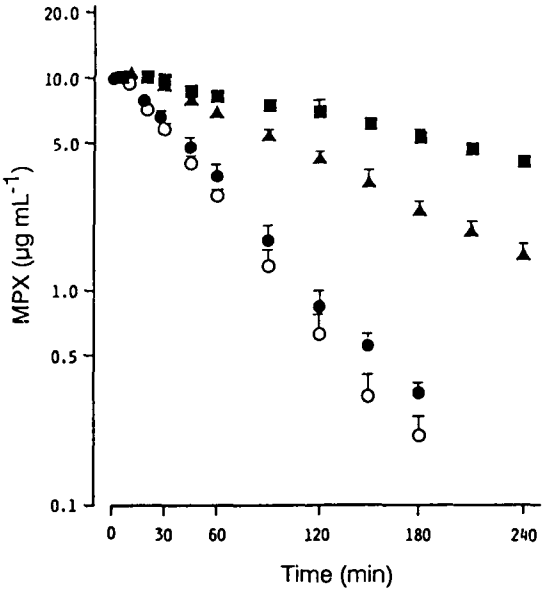



FIG. 1. Mean semilogarithmic plots of plasma concentration-time of 1-methyl-3-propylxanthine (MPX) in control (○) and enoxacin-pretreated (▲, 25 mg kg$^{-1}$; ■, 100 mg kg$^{-1}$) or NY-198-pretreated (●, 25 mg kg$^{-1}$) rats after a single intravenous administration of MPX, 2·5 mg kg$^{-1}$. Each point represents mean ± standard error (n = 4-5).

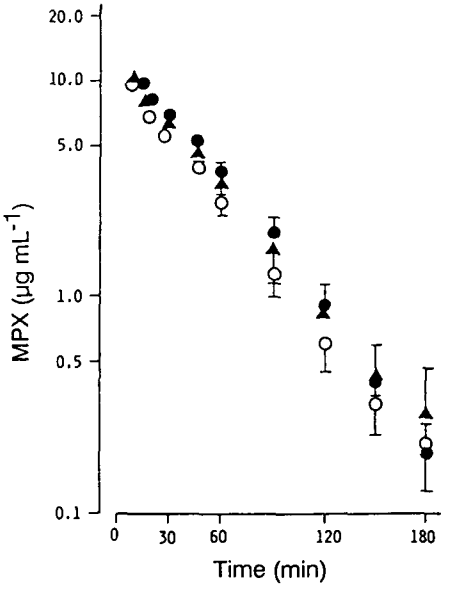



FIG. 2. Mean semilogarithmic plots of plasma concentration-time of MPX in control (○) and 4-oxoenoxacin-pretreated (▲, 5 mg kg$^{-1}$; ●, 20 mg kg$^{-1}$) rats after a single intravenous administration of MPX (2·5 mg kg$^{-1}$). Each point represents mean ± standard error (n = 4-5).

respectively, compared with the controls, suggesting that the total body clearance of MPX is reduced dose-dependently by the treatment with enoxacin. The effect of enoxacin on the protein binding of MPX was also examined. The protein binding was 96·5 ± 0·6% (without), 95·8 ± 0·9% (with 0·1 μg mL$^{-1}$), 96·0 ± 0·7% (with 1 μg mL$^{-1}$) and 96·6 ± 0·5% (with 5 μg mL$^{-1}$). There was no significant difference in the protein binding of MPX either in the presence or in the absence of enoxacin at various concentrations. This result is consistent with the findings that the apparent volume of distribution (V) of MPX was not significantly different between the control (0·212 ± 0·011 L kg$^{-1}$) and the treated groups (0·215 ± 0·006 and 0·238 ± 0·007 L kg$^{-1}$ for 25 and 100 mg kg$^{-1}$ enoxacin-treated groups, respectively). The MRT of MPX in the enoxacin-treated rats was shown to be 1·91 and 4·07 h for 25 and 100 mg kg$^{-1}$ enoxacin, respectively, which were significantly greater than those values obtained in the control rats (0·68 h). On the other hand, no significant changes were observed in any pharmacokinetic parameters of MPX after pretreatment with NY-198.

Fig. 2 shows the disappearance curve of MPX from plasma after pretreatment with and without 4-oxo-enoxacin, while Table 2 shows the pharmacokinetic parameters of MPX in these groups. Plasma concentrations of MPX in the 4-oxo-enoxacin treated group showed no significant change. No significant changes in the pharmacokinetic parameters of MPX were observed after pretreatment with 5 and 20 mg kg$^{-1}$ of 4-oxo-enoxacin. Plasma concentration of 4-oxo-enoxacin declined biexponentially (data not shown) and the mean plasma concentration after pretreatment with 20 mg kg$^{-1}$ of 4-oxo-enoxacin was 13·22 ± 1·25 μg mL$^{-1}$ at the first sampling time (20 min after administration) and 0·23 ± 0·07 μg mL$^{-1}$ at the last sampling time (190 min).

The disappearance curve of enprofylline from plasma after a single intravenous administration of 2·5 mg kg$^{-1}$ with and without enoxacin (100 mg kg$^{-1}$) and the pharmacokinetic parameters are shown in Fig. 3 and Table 3, respectively. No

Table 1. Pharmacokinetic parameters of 1-methyl-3-propylxanthine (MPX) after pretreatment with and without enoxacin or NY-198 in rats.

| Treatment | $K_{el}$(h$^{-1}$) | V (L kg$^{-1}$) | CL (L h$^{-1}$ kg$^{-1}$) | MRT (h) |
|---|---|---|---|---|
| Control | 1·503 ± 0·115 | 0·212 ± 0·011 | 0·312 ± 0·026 | 0·683 ± 0·054 |
| Enoxacin | | | | |
| 25 mg kg$^{-1}$ | 0·528 ± 0·033* | 0·215 ± 0·006 | 0·115 ± 0·011* | 1·905 ± 0·115* |
| 100 mg kg$^{-1}$ | 0·250 ± 0·023* | 0·238 ± 0·007 | 0·060 ± 0·006* | 4·072 ± 0·037*,** |
| NY-198 | 1·381 ± 0·195 | 0·203 ± 0·004 | 0·270 ± 0·033 | 0·742 ± 0·078 |

Values represent mean ± standard error (n = 4–5). * Significant difference between the control and the treated rats. ** Significantly different from the rats treated with 25 mg kg$^{-1}$ of enoxacin. Enoxacin and NY-198 were administered orally 1 h before intravenous administration of MPX, 2·5 mg kg$^{-1}$.

Table 2. Pharmacokinetic parameters of MPX after pretreatment with and without 4-oxo-enoxacin in rats.

| Treatment | $K_{el}(h^{-1})$ | V (L $kg^{-1}$) | CL (L $h^{-1}$ $kg^{-1}$) | MRT (h) |
|---|---|---|---|---|
| Control | 1·503±0·115 | 0·212±0·011 | 0·312±0·026 | 0·683±0·054 |
| 4-oxo-enoxacin | | | | |
| 5 mg $kg^{-1}$ | 1·435±0·255 | 0·194±0·004 | 0·271±0·046 | 0·740±0·141 |
| 20 mg $kg^{-1}$ | 1·321±0·144 | 0·198±0·013 | 0·249±0·013 | 0·747±0·079 |

Values represent mean ± standard error (n = 4–5). No significant difference between the control and the treated rats. 4-Oxo-enoxacin was administered intravenously 10 min before intravenous administration of MPX, 2·5 mg $kg^{-1}$.

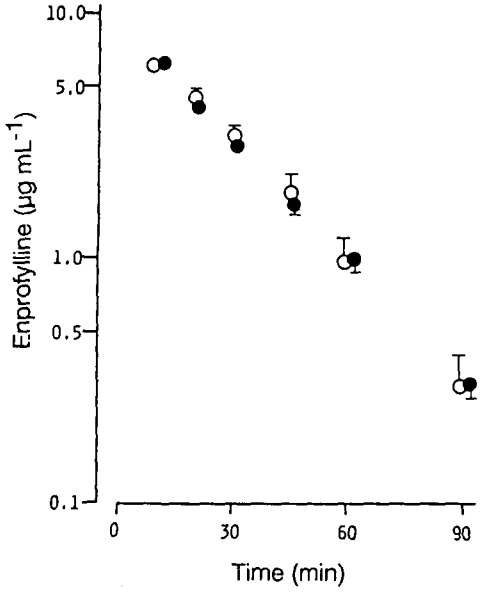



FIG. 3. Mean semilogarithmic plots of plasma concentration-time of enprofylline in control (○) and enoxacin-pretreated (●) rats after a single intravenous administration of enprofylline (2·5 mg $kg^{-1}$). Each point represents mean ± standard error (n = 4).

significant changes in the plasma concentrations and pharmacokinetic parameters between the control and the enoxacin-pretreated groups were observed.

## Discussion

Enoxacin is a potent inhibitor of theophylline clearance, and greatest inhibition occurs in combination with other drugs (Landay et al 1978; Jackson et al 1981; Zarowitz et al 1981; Marguis et al 1982; Jonkman & Upton 1984). To investigate the mechanism of interaction between theophylline and enoxacin, the present study was carried out in rats using xanthine derivatives, MPX and enprofylline, as models of theophylline. Our previous studies in rats demonstrated extremely low excretion of MPX in the urine, indicating that MPX is almost completely metabolized in the liver (Apichartpichean et al 1988). In contrast, enprofylline has been reported to be mainly excreted unchanged in the urine (Persson et al 1982). Thus, the elimination characteristics of the two drugs are different. From these observations, both drugs are considered to be useful as tools for clarifying the precise mechanism of the interactions in both liver and kidney between enoxacin and xanthine derivatives including theophylline.

This study clearly shows that enoxacin significantly reduces total body clearance of MPX but does not affect the pharmacokinetics of enprofylline. Also, the degree of reduction in the total body clearance of MPX after pretreatment with enoxacin is dependent on the dose of enoxacin. The percentage decrease of total body clearance of MPX after pretreatment with 25 mg $kg^{-1}$ of enoxacin observed in this study was larger than that observed for antipyrine with 50 mg $kg^{-1}$ of enoxacin (Edwards et al 1988). This could be due to the difference in the metabolism between MPX and antipyrine or the capacity-limited hepatic metabolism of MPX which has characteristics of a dose-dependent disposition and concentration-dependent binding to plasma protein (Hasegawa et al, unpublished data). However, the present study used a dose of MPX which shows linear elimination kinetics. The results clearly show that enoxacin does not possess the ability to displace MPX from its binding sites in rat albumin, although plasma protein binding of MPX in rats is higher than that of theophylline (Apichartpichean et al 1988, 1989). This supports other studies in which the protein binding of enoxacin and NY-198 has been reported to be low at approximately 30% (Okezaki et al 1988).

Approximately 90% of the total body clearance of theo-

Table 3. Pharmacokinetic parameters of enprofylline after pretreatment with and without enoxacin in rats.

| Treatment | $K_{el}$ ($h^{-1}$) | V (L $kg^{-1}$) | CL (L $h^{-1}$ $kg^{-1}$) | MRT (h) |
|---|---|---|---|---|
| Control | 2·337±0·248 | 0·266±0·006 | 0·608±0·064 | 0·423±0·051 |
| Enoxacin | 2·285±0·125 | 0·277±0·011 | 0·615±0·023 | 0·429±0·023 |

Values represent mean ± standard error (n = 4). No significant difference between the treatments. Enoxacin was administered orally 1 h before intravenous enprofylline 2·5 mg $kg^{-1}$.

phylline in man is due to biotransformation in the liver. The biotransformation of theophylline in rats, however, has been reported to be about 50% by $N^3$-demethylation and by oxidation (Williams et al 1979). It has been shown that these metabolic pathways occur in the hepatic mixed-function oxidase system (cytochrome P450) (Jenne et al 1976; Grygiel & Birkett 1981; Grygiel et al 1984). It has also been postulated that the metabolic pathways of other well known xanthine derivatives, caffeine and theobromine, also take place in the hepatic mixed-function oxidase system by *N*-demethylation and oxidation (Miners et al 1985; Campbell et al 1987). Indeed, the chemical structure of MPX is very similar to that of theophylline, which has an alkyl group (n-propyl) at the $N^3$ position of the 1-methylxanthine molecule. Considering these points, it might be speculated that the main metabolic pathway of MPX in rats is solely by oxidation ($C^8$-oxidation or $N^3$-alkyloxidation), since the pathways of theophylline metabolism in rats are $N^3$-demethylation to 1-methylxanthine and oxidation to 1,3-dimethyluric acid (Williams et al 1979). $N^3$-Depropylation, then, might not occur in the hepatic mixed-function oxidase system.

Beckmann et al (1987) have reported that enoxacin selectively inhibits the elimination process of theophylline depending on cytochrome P450 isozymes for *N*-demethylation in man. The present study, however, clearly shows the strong inhibitory effect of enoxacin on the metabolism of MPX. Based on these observations, we propose that enoxacin does not solely inhibit the elimination process depending on cytochrome P450 isozymes for *N*-demethylation.

In addition, it was found that a high dose of the enoxacin metabolite, 4-oxo-enoxacin, has a tendency to decrease total body clearance of MPX, although 4-oxo-enoxacin has no influence on disposition of antipyrine in rats (Edwards et al 1988). It appears that a dose (20 mg $kg^{-1}$) of its metabolite, 4-oxo-enoxacin, is at least as high as from enoxacin since the low dose (5 mg $kg^{-1}$) did not affect the pharmacokinetics of MPX and the urinary recovery of 4-oxo-enoxacin is approximately 15% of a dose of enoxacin (Wijnands et al 1986). For these reasons, it may be concluded that 4-oxo-enoxacin has little or no influence on the disposition of MPX.

Wijnands et al (1986) proposed that the 4-oxo groups of quinolones excreted in the urine are the main cause of the change in theophylline clearance. This hypothesis remains to be clarified. Recent findings in man using caffeine have provided further evidence that different molecular and spatial structures of various quinolones are responsible for the differences in inhibitory potency (Harder et al 1988; Carbo et al 1989). Our previous studies in man demonstrated that a newly developed quinolone, T-3262 (Tosufloxacin tosilate; (±)-7-(3-amino-1-pyrrolidinyl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid *p*-toluenesulphonate hydrate), which does not form a 4-oxo metabolite, has a moderate inhibitory effect (30%) on theophylline clearance (Takagi et al 1988b). NY-198, which does not yield a 4-oxo metabolite, does not affect the pharmacokinetics and metabolism of theophylline in man (Kuzuya et al 1989).

On the other hand, it has been reported that enoxacin inhibits the tubular secretion of theophylline metabolites, 1-methyluric acid, 3-methylxanthine and 1,3-dimethyluric acid, in man due to the competition for renal tubular secretion (Beckmann et al 1987). Sano et al (1989) suggest that the inhibitory effect of enoxacin on the renal excretion of theophylline in man is due to an increase in net reabsorption. It is possible that there is an interaction between enprofylline and enoxacin in the kidney since enprofylline is almost completely excreted in the urine in an unchanged form by tubular secretion (Persson et al 1982; Lunell et al 1984; Borga et al 1986; Lunell & Borga 1987). Unexpectedly, the present study demonstrated no significant changes in the pharmacokinetic parameters of enprofylline even with pretreatment with a large dose of enoxacin (100 mg $kg^{-1}$). The results of the present study may suggest that enoxacin is unlikely to affect renal excretion of theophylline-like xanthine derivatives in rats.

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