Effect of Norfloxacin on Theophylline Disposition: A Comparison with Other Fluoroquinolones

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The effects of norfloxacin (NOR), at steady-state plasma concentrations of 0–32 mg · l^{-1}, on the plasma clearance of a 6 mg · kg-l iv bolus dose of theophylline (THEO) in the male Sprague-Dawley rat have been studied. The effects were characterised by a Ki value (Ki = 12 μM), which was comparable with Ki values obtained previously under identical conditions for ciprofloxacin, but higher than that obtained for enoxacin. The distributional characteristics, volume of distribution and liver to plasma concentration ratio, were very similar for the three compounds. The only marked pharmacokinetic differences were in hepatic clearance, where there was a rank order NOR > ciprofloxacin > enoxacin, a reverse of the order in the reduction of THEO clearance seen in clinical studies. The advantages of using the steady-state experimental design described here are that equivalent concentrations are utilised to compare related drugs and differences in pharmacokinetics are accounted for, to allow a direct comparison of potency. This information, together with additional pharmacokinetic considerations, suggests that the different effects on THEO clearance seen in the clinic for NOR, ciprofloxacin and enoxacin are not solely due to differences in inhibitory potency, but also involve differences in hepatic clearance and hence systemic availability of the fluoroquinolones.

KEY WORDS: norfloxacin; theophylline; pharmacokinetics; drug–drug interactions; ciprofloxacin; enoxacin.

INTRODUCTION

Fluoroquinolone antibiotics can affect the disposition of theophylline (THEO), by inhibition of its metabolism at the liver microsomal level (1,2). However, the degree to which individual fluoroquinolone affects THEO in clinical studies varies markedly (3). Norfloxacin (NOR) has been shown to have little effect on THEO, whereas enoxacin and ciprofloxacin have been shown to reduce THEO plasma clearance by 74 and 33%, respectively. We have recently shown (4) that there was little difference in the inhibition of THEO metabolism or ethoxycoumarin O-de-ethylase in rat liver microsomes, between NOR, ciprofloxacin or enoxacin. The question of whether the lack of inhibition of NOR seen in the clinical setting arises from the differences in the inhibitory ability of NOR towards cytochrome P450 or from pharmacokinetic issues such as bioavailability and distribution remains to be resolved. To this end we have designed experiments where plasma concentrations of NOR are maintained at steady-state by intravenous (iv) infusion following an iv bolus loading dose and the disposition of a single iv bolus dose of THEO is monitored in plasma. This method allows the comparison of the relative potencies of the fluoroquinolones, as any pharmacokinetic differences between the fluoroquinolones are 'designed out'. We have previously described experiments where a similar approach has been used to determine in vivo Ki values for enoxacin and ciprofloxacin (5).

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MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats were obtained from the University of Manchester Biological Services Unit, housed 2–3 per cage on a bedding of sawdust and fed with CRN rat diet. They has access to water *ad libitum*. The holding room was kept in a constant range of 20–21°C and alternated between 12 hours of light and darkness.

Polyethylene cannulae were inserted, under halothane anaesthesia, into the (right) jugular vein and carotid artery (6). All cannulations were performed during the afternoon of the day before the experiment, the animals therefore having about 18 hours recovery from the surgery. Once the animals had been cannulated, they were housed individually.

Preliminary Disposition Studies

Values for the primary pharmacokinetic parameters clearance (CL) and volume of distribution (V) describing the disposition of NOR in rats have not been reported previously. Therefore a preliminary study was undertaken to determine CL and V utilising short iv fusions. This method reduced the dependence of the pharmacokinetic parameters on the extrapolated fraction of the area under plasma concentration-time curve (AUC), when compared with single intravenous bolus doses.

Animals (239–269 g, n = 6) received NOR, dissolved in 0.1 M NaOH to 15 mg · ml^{-1}, either 42 mg · kg^{-1} at 1.05 mg · min^{-1} or 60 mg · kg^{-1} at 0.25 mg · min^{-1}, *via* the venous cannula. Blood samples (n = 11) were taken during and after infusion, to allow estimation of both the approach to steady-state and the fall-off curve. Sampling was performed from the carotid artery over a period of four hours.

Steady State Studies

Mean values of CL and volume of distribution at steady-state (Vss) calculated from the preliminary disposition studies were used in the steady-state studies. To achieve the desired steady-state plasma concentration (Css), a bolus of fluoroquinolone, calculated using the relationship

$$Dose = V_{ss} \cdot C_{ss}$$

was given *via* the venous cannula. This was followed immediately by an infusion of fluoroquinolone (R_0), which was calculated for the desired steady-state concentration using the relationship

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$$R_0 = CL \cdot C_{ss}$$

A bolus dose of 1.8mg THEO (6 mg · ml^{-1} in distilled water) was given, followed by a suitable bolus dose of NOR, after flushing the cannula with heparinised saline (100 units · ml^{-1}). The infusion rate was limited by the solubility of NOR in 0.1 M NaOH, which was 15 mg · ml^{-1}; the flow rate was either 0.15 or 1.0 ml · h^{-1}. A range of NOR concentrations were studied (0.47–32.0 mg · l^{-1}) and the clearance of THEO was assessed at each different concentration of NOR (n = 30). Each experimental group also contained a control rat receiving an infusion of the solvent containing no NOR. Blood was collected into Eppendorf tubes containing one or two drops of heparinised saline (500 units · ml^{-1}) over a period of six hours. Plasma was separated and stored at 4°C until analysis, usually on the following day.

HPLC-Analytical Methods

The analytical methodology has been described elsewhere in more detail (7). Briefly, plasma was extracted using dichloromethane: isopropanol after adjustment of pH with saturated $NaHCO_3$ solution, evaporated and reconstituted in mobile phase. HPLC with UV detection was used to identify the analytes, with a wavelength of 280 nm. The method allowed the simultaneous assay of both NOR and THEO in the same run. The limits of quantification were 0.5 mg · l^{-1} for NOR and 1.0 mg · l^{-1} for THEO.

Tissue Distribution Studies

To assess the liver: plasma concentration ratio of NOR the livers were removed from animals that had taken part in the steady-state infusion experiments, after they had been killed by cervical dislocation. Data for ciprofloxacin and enoxacin were also obtained, from similar experiments described previously (5). The livers were washed in normal saline solution, to remove any clots, blotted dry and weighed, before storing at −20°C until analysis. The assay method was based on that previously described (7) and involved taking liver tissue (100 mg), and grinding together with standard $NaHCO_3$ solution (1.0 ml) and internal standard solution (100 µl). This was extracted with CH_2CL_2: isopropanol (5.0 ml) twice. The combined organic layers were evaporated and reconstituted in mobile phase before HPLC analysis.

Tissue to plasma concentration ratios (K_p) were calculated as the ratio of plasma concentration at the last time point to the liver concentration in tissue. The estimates of K_p were corrected for CL_H in the following manner (8). $K_{p,corr} = K_p/(1 - E)$, where E is hepatic extraction ratio (= CL_H/Q_H, where $Q_H = 5.31 \cdot h^{-1}kg^{-1}$). Plasma protein binding as measured by fraction unbound (fu) of the fluoroquinolones was obtained from literature estimates (9,10), thus the unbound fraction in liver (fu_L) = $fu/K_{p,corr}$.

Urinary Recovery Of Fluoroquinolones and Calculation Of Hepatic Clearance

To investigate the role of renal excretion in the pharmacokinetics of NOR, enoxacin and ciprofloxacin in the rat, a limited number of experiments were performed to estimate the fraction of dose excreted unchanged in the urine.

Three groups of animals (n = 6–8) were cannulated in the jugular vein and left to recover for about six hours. Fluoroquinolone (35–90 mg · kg^{-1}) was administered intravenously *via* the cannula and the animals housed in individual metabolism cages for 24 hours. Urine was collected and stored at −20°C until analysis. The assays were based on those described previously (7). Urine was diluted 25–50 fold to achieve concentrations in the linear range of each assay. The fraction excreted unchanged in the urine (fe) was calculated as the ratio of the amount recovered over the dose administered – a mean estimate of renal clearance (CL_R) was calculated as fe · CL, CL being obtained from the steady state experiments. Hepatic clearance (CL_H) was then calculated as the difference between total plasma clearance and CL_R. Unbound liver clearance ($CL_{H,u}$) was calculated as fu · CL_H.

Data Analysis

Convolution of a simple exponential disposition function with a zero order input function yields the description of the plasma concentration-time data obtained in the preliminary studies [equation 1]:

$$C = \frac{Dose}{\tau} \sum_{i=1}^{n} \left(\frac{1 - e^{+\theta\lambda_i}}{-\lambda_i} \right) C_i' e^{-\lambda_i t} \qquad [1]$$

Where τ is the infusion duration, $C_i' = C_i/Dose$ and $\theta = t$ for $t \leq \tau$, $\theta = \tau$ for $t \geq \tau$.

$$\text{Thus } CL = \frac{Dose}{\sum_{i=1}^{n} \frac{C_i}{\lambda_i}}, \quad MRT = \frac{\sum_{i=1}^{n} \frac{C_i}{\lambda_i^2}}{\sum_{i=1}^{n} \frac{C_i}{\lambda_i}}, \quad \text{Vss} = \text{CL·MRT}.$$

Model [1] was fitted to the data using the Siphar program (version 3.3, Simed, Créteil, France). Two exponentials were required to obtain the best fits, with a weighting of $1/y_{(calc)}$.

The relationship between NOR plasma concentration and infusion rate appeared to be nonlinear and was modelled using a modification of the Michealis-Menten equation [equation 2]. A weighting scheme of $1/y_{(calc)}^2$ was required to obtain the best fit (Siphar).

$$C_{ss} = \frac{R_0 K_m}{V_{max} - R_0} \qquad [2]$$

Total plasma clearance of THEO was estimated in the steady-state experiments after fitting a simple iv model [equation 3] to the plasma concentration-time data (Siphar):

$$C = \sum_{i=1}^{n} C_i e^{-\lambda_i} \qquad [3]$$

One exponential only was required—generally a weighting scheme of $1/y_{(calc)}$ gave the best fits of the model to the data.

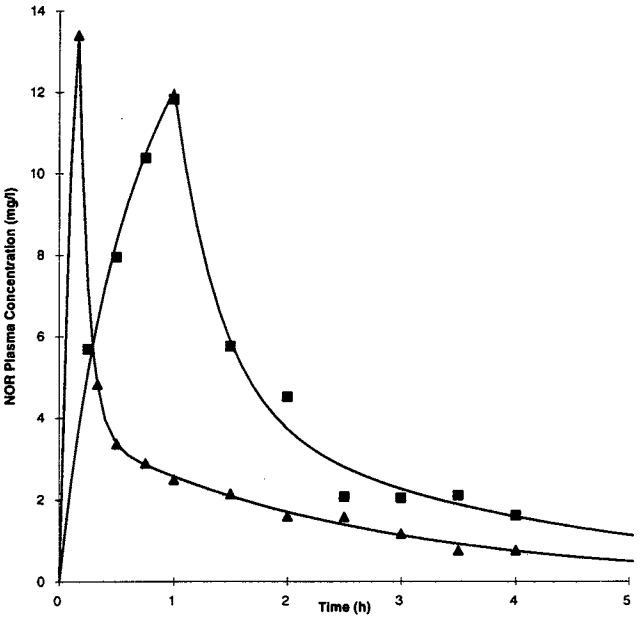

Figure 1 Typical NOR plasma concentrations following short iv infusions. ▲—42 mg · kg^{-1} over 10 minutes, ■—60 mg · kg^{-1} over 60 minutes

The relationship between THEO clearance and NOR steady-state concentration was described by the model [equation 4] previously described (5), using a weighting of $1/y_{(calc)}$:

$$CL_{obs} = \frac{CL_1}{\left(1 + \frac{C_{ss}}{K_i}\right)} + CL_2 \qquad [4]$$

where CL_1 is the portion of total clearance affected by fluoroquinolone, Css is the steady-state plasma fluoroquinolone concentration, CL_2 is the unaffected portion of total clearance and Ki is the concentration of fluoroquinolone that is required to make CL_1 fall to 50% of its initial value.

RESULTS

Disposition of NOR

Typical concentration-time profiles are shown in Figure 1 for the two dose levels studied. The results obtained from model fitting are shown in Table I. Nakamura *et al.* (9) found that the elimination half life was 2.35 h after oral dosing in male Wistar rats. The terminal half life reported here is comparable, at about 1.8 h. The purpose of the preliminary experiment was to estimate the primary pharmacokinetic parameters CL and V_{ss}. From data obtained, it was decided to use a value of 2.7 l · h^{-1} · kg^{-1} for CL and 5.5 l · kg^{-1} for V_{ss}. These values enabled the design of infusion regimes of NOR to achieve and maintain a steady-state plasma concentration.

The relationship between steady-state plasma concentration of NOR and infusion rate appeared to be linear at infusion rate less than 15 mg · h^{-1} · kg^{-1}, but it was found that clearance fell at higher infusion rates (Figure 2). The clearance of NOR at the low infusion rates was found to be 2.4 l · h^{-1} · kg^{-1}, which was in good agreement with the value obtained from the preliminary experiments. Modelling of the nonlinear relationship (equation [2]) between NOR steady-state concentration and infusion rate gave estimates (± SE) of V_{MAX} as 77.9 ± 12.2 mg · h^{-1} · kg^{-1} and K_M as 39.4 ± 8.0 mg · l^{-1}. The nonlinear model described the data better than a simple linear relationship, despite a high correlation between V_{MAX} and K_M, reflecting an inability in the model to accurately predict the parameters independently. This was due to the experiments being performed at lower steady-state concentrations than the predicted K_M. This nonlinear pharmacokinetic behaviour, which is marked at the higher infusion rates may be due to saturation of renal secretion or metabolic pathways.

The ability of the loading doses to achieve the required initial plasma concentrations indicated the success of the preliminary experiments in the estimation of Vss. Tables II and III summarise a number of pharmacokinetic parameters for the three fluoroquinolones. It can be seen that, whilst enoxacin has the lowest CL and Vss, there are no large differences in the primary pharmacokinetic parameters. However, there are significant differences ($p < 0.05$) in fe and in CL_H. Table III summarises distributional characteristics for the fluoroquinolones, where there are no differences between the three compounds. The Kp is similar for the three compounds and fu_L, a measure of liver binding, differs only approximately two-fold. It is interesting to compare NOR and enoxacin, where tissue binding is similar, but metabolic clearance is markedly different, occurring to a much greater extent for NOR. Thus although the binding in the liver of enoxacin is comparable, it undergoes metabolism to a much lesser degree, resulting in a three to five fold difference in unbound hepatic clearance (Table II). Ciprofloxacin is intermediate in terms of $CL_{H,u}$ and is comparable in liver binding.

Effect Of Norfloxacin on Theophylline Clearance

Typical plasma concentration-time curves are shown in Figure 3, for NOR and THEO. The clearance of THEO was found to decrease with increasing NOR concentration; this

Table I. Estimates of Pharmacokinetic Parameters[a] for Norfloxacin Using Short Infusion Experiments

Dose	C_1 (mg · l^{-1})	λ_1 (h^{-1})	C_2 (mg · l^{-1})	λ_2 (h^{-1})	$t_{1/2\beta}$ (h)	MRT (h)	CL (l · h^{-1} · kg^{-1})	V_{ss} (l · kg^{-1})
42 mg · kg^{-1}	16 ± 6	9.2 ± 2.0	4.2 ± 1.5	0.40 ± 0.01	1.7 ± 0.1	2.1 ± 0.1	3.75 ± 1.30	7.2 ± 1.8
60 mg · kg^{-1}	25 ± 4	4.5 ± 1.8	6.5 ± 1.5	0.37 ± 0.04	1.9 ± 0.2[b]	2.1 ± 0.2[b]	2.66 ± 0.06[b]	5.5 ± 0.6[b]

[a] Mean data (n = 3) ± SD.
[b] No statistical difference between doses.

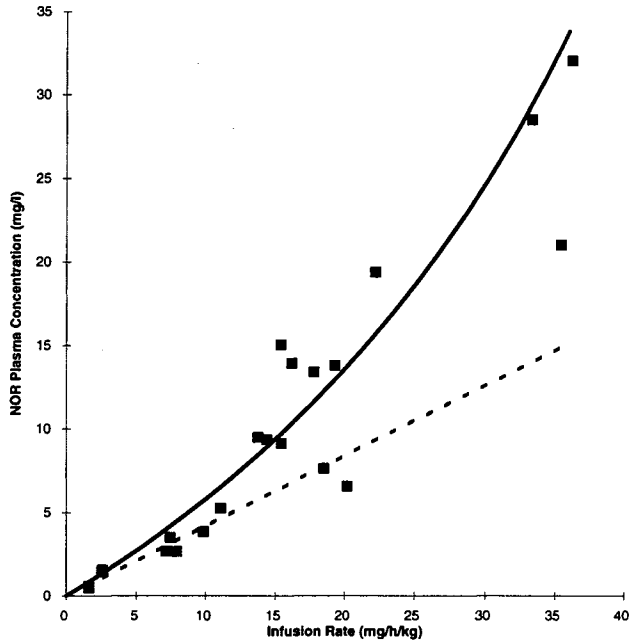

Figure 2 Effect of infusion rate on NOR plasma concentrations. Data from 30 animals are shown. The dashed line indicates a linear clearance estimate of 2.4 $l \cdot h^{-1} \cdot kg^{-1}$ (applicable to concentrations lower than 15 $mg \cdot l^{-1}$) and the solid line the nonlinear clearance (V_{MAX} 77.9 $mg \cdot h^{-1} \cdot kg^{-1}$ and K_M 39.4 $mg \cdot l^{-1}$) over the full concentration range

relationship was nonlinear and fell to a minimum value above steady-state concentrations of about 20 $mg \cdot l^{-1}$. Figure 4 shows the relationship between steady-state concentration of NOR and THEO clearance. The parameter estimates (± SE) of the fitted model were CL_1 = 50 ± 1.0 $ml \cdot h^{-1}$, CL_2 = 6.2 ± 0.7 $ml \cdot h^{-1}$ and Ki = 3.9 ± 0.3 $mg \cdot l^{-1}$ (12.1 μM). The sum of the two clearance terms (56.2 $ml \cdot h^{-1}$) is the clearance of THEO in the absence of NOR. CL_2, the residual value of clearance, compares favourably across all three fluoroquinolone studies and represents renal clearance of THEO. We have confirmed the renal excretion of THEO in our laboratory (4) to account for approximately 20% of a 6 $mg \cdot kg^{-1}$ dose, thus CL_R is about 11 $ml \cdot h^{-1}$.

DISCUSSION

NOR was found to be a relatively potent inhibitor (Ki = 12 μM) of THEO clearance in the rat and comparable to

Table II. Comparison of Pharmacokinetic Data Describing the Elimination of NOR, Ciprofloxacin and Enoxacin

	Norfloxacin	Ciprofloxacin	Enoxacin
CL ($l \cdot h^{-1} \cdot kg^{-1}$)[a]	2.7 ± 0.1	2.2 ± 0.4[b]	1.7 ± 0.1[b]
MRT (h)[a]	2.1 ± 0.1	1.7 ± 0.2[b]	1.9 ± 0.5[b]
fe[a]	0.15 ± 0.07	0.30 ± 0.08	0.56 ± 0.08
CL_H ($l \cdot h^{-1} \cdot kg^{-1}$)	2.2	1.5	0.7
$CL_{H,u}$ ($l \cdot h^{-1} \cdot kg^{-1}$)	0.92	0.51	0.17–0.29

[a] Mean data (±sd).
[b] Data from Davis *et al.* (5).

Table III. Comparison of Pharmacokinetic Data Describing the Distribution of NOR, Ciprofloxacin and Enoxacin

	Norfloxacin	Ciprofloxacin	Enoxacin
Vss ($l \cdot kg^{-1}$)[a]	5.5 ± 0.6	4.0 ± 0.7[b]	3.1 ± 0.7[b]
K_p[a]	2.5 ± 0.9	3.7 ± 1.5[b]	4.7 ± 1.3[b]
$K_{p,corr}$	4.3	5.1	5.4
fu	0.42[c]	0.34[d]	0.24–0.41[e]
fu_L	0.10	0.07	0.04–0.08

[a] Mean data (±sd).
[b] Davis *et al.* (5).
[c] Nakamura *et al.* (9).
[d] Siefert *et al.* (10).
[e] Okezaki *et al.* (11).

ciprofloxacin in similar experiments (5). We have previously shown (5) enoxacin to be more potent than ciprofloxacin. These results on first sight are not fully compatible with the large differences seen in clinical studies investigating the interaction of fluoroquinolones with THEO. Table IV compares our Ki estimates obtained in the rat with the changes in THEO pharmacokinetics seen in clinical studies; in the latter there is a clear rank order enoxacin > ciprofloxacin > NOR, yet these pronounced differences are not seen in the rat Ki values.

It is interesting to note that the distributional characteristics of these three fluoroquinolones in the rat are very similar. Both Vss and liver Kp show close agreement between three compounds (Table III). The only marked differences seen in the pharmacokinetics of these compounds were in hepatic clearance, where there is a rank order NOR > cip-

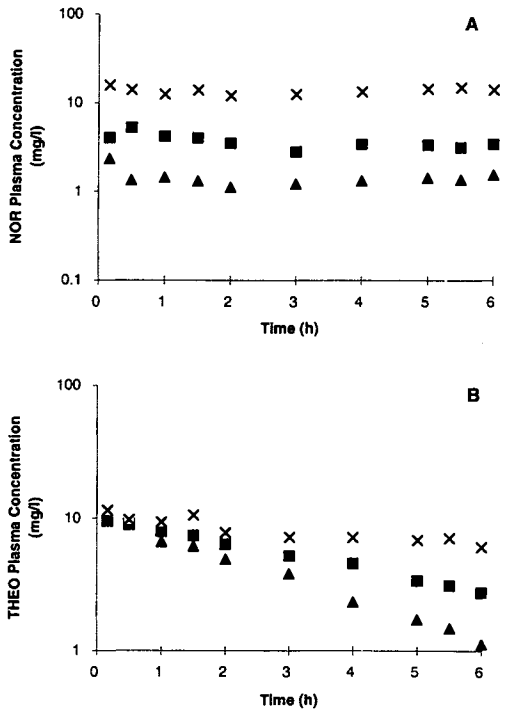

Figure 3 Typical NOR steady state concentration-time data. ▲—1.4 $mg \cdot l^{-1}$, ■—3.8 $mg \cdot l^{-1}$, × −13.8 $mg \cdot l^{-1}$. Figure 3B Typical THEO concentration-time data in the presence of NOR. ▲—0 $mg \cdot l^{-1}$, ■—3.8 $mg \cdot l^{-1}$, × −13.8 $mg \cdot l^{-1}$ NOR

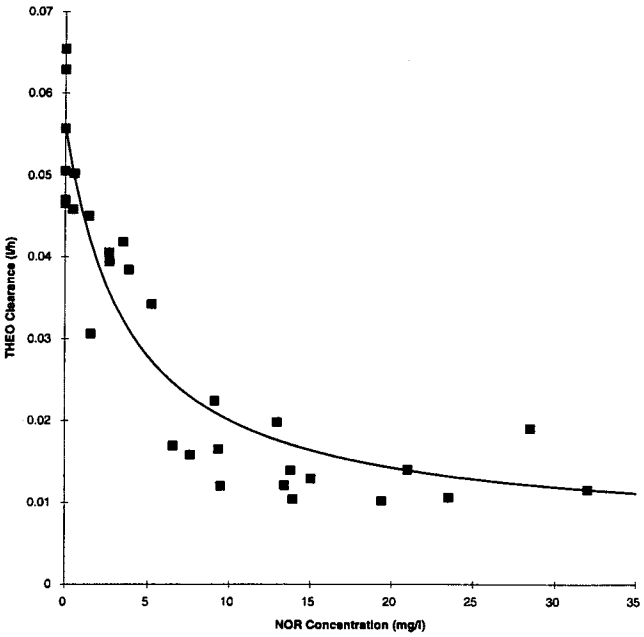

Figure 4 Effect of NOR concentration on THEO clearance. Data from 30 animals which can be described by equation [5], with a Ki estimate of 3.9 mg · l^{-1}

rofloxacin > enoxacin (Table II), a reverse of the rank order in the reduction of THEO clearance seen in clinical studies.

In man, the urinary recovery of NOR (27%) is about half that of ciprofloxacin and enoxacin, with renal clearance values for all three fluoroquinolones being in excess of renal glomerular filtration rate, after correction for protein binding (13,14). We have found broadly similar results in the rat, with the rank order being the same as that described above for CL_H in the rat. Unfortunately there are no adequate iv data reported in the literature to obtain comparable clearance estimates in man.

Also shown in Table IV is a comparison of AUC following a single oral 400 mg dose of NOR, ciprofloxacin and enoxacin administered to man. In addition to measuring CL, AUC reflects availability and thus exposure to drug. Enoxacin has a fivefold higher AUC from a single 400 mg dose than NOR and this larger exposure (which presumably is a reflection of a low hepatic clearance, as seen in the rat)

Table IV. Comparison of Inhibitory Effects of Fluoroquinolones in Rat and Man

	Norfloxacin	Ciprofloxacin	Enoxacin
Ki, μM (rat)	12.1	16.3[a]	4.7[a]
% fall in THEO clearance[b]	15	30	60
$AUC_{0-\infty}$ (μmol · h · l^{-1})[c]	12–20	17–24	50–90

[a] Data from Davis *et al.*, (4).
[b] Data from Edwards *et al.*, (3).
[c] Data for a 400 mg single oral dose, adapted from Paton & Reeves (12).

would account for the larger effect seen with enoxacin in the clinic. Rogge *et al.* (15) have shown that the effect of enoxacin on THEO clearance is dose dependent. The increased exposure would be exaggerated at the level of the liver by the differences in unbound hepatic clearance. Thus the rank order observed in the clinic probably reflects mainly fluoroquinolone concentration rather than inhibitory potential.

It is also informative to compare *in vitro* inhibitory experiments with the clinical results. We have estimated Ki values for 1,3 dimethyl uric acid production from THEO in rat liver microsomes to be 0.5–1.0 mM for the three fluoroquinolones studied here (4). Sarkar et al. (2) have estimated *in vitro* Ki values for enoxacin using human liver microsomes, also with THEO as a substrate, to be 0.3, 0.1 and 3.4 mM for 3-methylxanthine, 1-methylanthine and 1,3 dimethyl uric acid respectively. As peak plasma concentrations of fluoroquinolones are generally less than about 0.020 mM (7 mg · l^{-1}), the concentrations at the sites of THEO metabolism in the liver required for inhibition must exceed plasma concentrations markedly. However, considering these Ki values on a purely relative level, there is little difference between NOR, enoxacin and ciprofloxacin.

The advantages of using the experimental design described here are that equivalent concentrations are utilised to compare related drugs and differences in pharmacokinetics have been designed out, to allow a direct comparison of potency. As these conditions are not observed in clinical usage of the fluoroquinolones, differences in circulating concentrations must be taken into account. Enoxacin has the largest effect in vivo as a single oral dose leads to a greater exposure to drug and this combined with a lower CL_H explains its larger clinical interaction. The low NOR concentrations suggest low systemic availability as the major factor for the low inhibitory effect on THEO metabolism seen in clinical studies.

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