

4-Quinolones Inhibit Biotransformation of Caffeine

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Summary. The pharmacokinetics of caffeine, including formation of its major metabolite paraxanthine in plasma, has been investigated in 12 healthy males (age 20–40 years) alone and during co-administration of the 4-quinolones ofloxacin, norfloxacin, pipemidic acid, ciprofloxacin, and enoxacin; ciprofloxacin and enoxacin were given in 3 different dose levels.

The naphthyridine derivative enoxacin and the pyrido-pyrimidine derivative pipemidic acid had caused marked inhibition of caffeine and paraxanthine metabolism, whereas the genuine quinolone derivatives norfloxacin and ciprofloxacin had little effect, and the pyrido-benzoxazine derivative ofloxacin had no detectable effect.

The different molecular and spatial structures of the compounds appear to be responsible for the differences in inhibitory potency.

Key words: caffeine, quinolones; paraxanthine, enoxacin, ciprofloxacin, pipemidic acid, norfloxacin, drug interaction, pharmacokinetics, drug metabolism, ofloxacin

Some bacterial DNA gyrase inhibitors of the 4-quinolone type cause a decrease in the clearance of theophylline, e.g. enoxacin [2, 21, 32, 33], ciprofloxacin [3, 19, 22, 25, 33], pipemidic acid [23] and pefloxacin [37], whereas other quinolone derivatives have little or no effect, e.g. ofloxacin [11, 12, 33], and nalidixic acid [33]. In contrast to treatment with the drug theophylline, the intake of caffeine is ubiquitous and not controllable. Therefore, interactions of 4-quinolones with “hidden” caffeine could be interpreted as side effects of quinolones, since the excitatory effects on the human CNS are the same for both groups of drugs [10, 13]. Like theophylline, the kinetics of caffeine are altered in cirrhosis, congestive heart disease and by drugs [4, 6, 34]. The elimination processes of caffeine and theo-

phylline are similar and depend on cytochrome P-450 mediated isoenzymes for N-demethylation and 8-hydroxylation in the human liver [8]. Caffeine is therefore suggested as a model compound to study and compare the interaction profiles of quinolones with other drugs undergoing hepatic biotransformation, such as the methylxanthines.

The pharmacokinetics of caffeine and paraxanthine, its major metabolite in man, have been investigated before and during treatment with several commonly available quinolones (Table 1), in two studies in different volunteers. Some of the results have already been published [29, 30].

The aims of the studies were:

- to evaluate the relationship between the interactive potency of quinolones and differences in their molecular structure
- to evaluate the dose-dependency of the inhibitory effects of enoxacin and ciprofloxacin, which are recommended to be given in a wider therapeutic dose range
- to obtain an insight into those stages of the metabolic pathway of caffeine and aspects of its kinetic disposition where quinolones might exert their inhibitory action.

Table 1. Treatment regimens with the quinolones

Quinolone	Abbreviation (Tables 3, 4)	Dose mg b. d.
Ofloxacin	OFL ^a	200
Norfloxacin	NOR ^b	400
Pipemidic acid	PPA ^b	400
Ciprofloxacin	CIP 1 ^b	100
	CIP 2 ^a	250
	CIP 3 ^b	500
Enoxacin	ENX 1 ^b	100
	ENX 2 ^b	200
	ENX 3 ^a	400

^a Study I ^b Study II

Table 2. Study protocol

Before trial	36-h methylxanthine-free diet (no tea, coffee, chocolate)
Day 1 (morning)	1: plasma sample (control value) 2: 230 mg caffeine oral 3: plasma samples over 24 h
2 (morning)	quinolone treatment commenced after last plasma sample
2 (evening)	next quinolone dose
3 and Day 4	quinolone b.d.
5 (morning)	1: plasma sample (control value) 2: 230 mg caffeine oral 3: last dose of quinolone given 4: plasma samples over 24 h
Day 6 (morning)	last plasma sample
2-week wash-out phase, then start of a new trial with the next quinolone, in randomized sequence	

Material and Methods

Subjects and Study Design

In two consecutive studies, each in 12 healthy male volunteers (age 20–40 years), the pharmacokinetics of caffeine and its major metabolite paraxanthine alone and at the end of 4 days of treatment with several quinolones (Table 1) were investigated. All participants were informed about the study and gave their written consent to participation in it.

Caffeine and paraxanthine concentrations in plasma were simultaneously determined after a single oral dose of 230 mg caffeine in a liquid preparation. Blood samples were collected 0.5, 1, 2, 4, 6, 10, 14, 20 and 24 h after the administration of caffeine.

Quinolones were given after completion of the caffeine-alone phase. All subjects received quinolones b.d. for 3 days. On the fourth day a last single dose of the quinolone was given together with a second dose of caffeine, followed by a further 24-h blood sampling period.

The volunteers were maintained on a methylxanthine-free diet (no tea, coffee or chocolate) from 36 h before the first dose of caffeine until the end of the second sampling period. The study design is illustrated in Table 2. The entire procedure in each subject was repeated for each quinolone after a two week wash out period, in a randomized sequence.

The investigation comprised two studies, one in 1986 and the other in 1987. The latter was performed to evaluate the dose-dependency and relation to structure of the effects demonstrated in the first study [29, 30].

Table 3. Mean (SD) kinetic parameters of Caffeine alone and during treatment with quinolone antibiotics ($n=12$; Wilcoxon matched pairs sign rank test)

Parameter ^a		Alone		During		
		x	(SD)	x	(SD)	
OFL	$t_{1/2el}$	2.9	(0.7)	2.8	(1.0)	NS
	AUC	20.6	(8.4)	20.3	(8.4)	NS
	t_{max}	0.83	(0.44)	0.68	(0.26)	NS
	C_{max}	4.09	(0.86)	4.34	(1.08)	NS
NOR	$t_{1/2el}$	3.2	(1.1)	3.7	(1.1)	$p<0.05$
	AUC	21.4	(9.8)	24.9	(10.0)	NS
	t_{max}	0.60	(0.20)	0.80	(0.30)	NS
	C_{max}	4.33	(0.79)	4.37	(0.85)	NS
PPA	$t_{1/2el}$	3.3	(1.1)	7.3	(3.2)	$p<0.001$
	AUC	21.8	(8.7)	60.8	(27.3)	$p<0.001$
	t_{max}	1.10	(0.60)	2.00	(1.70)	NS
	C_{max}	3.86	(0.55)	5.17	(0.83)	$p<0.001$
CIP 1	$t_{1/2el}$	3.4	(1.2)	3.6	(1.5)	NS
	AUC	21.4	(9.2)	25.0	(9.8)	NS
	t_{max}	1.00	(0.50)	1.00	(0.50)	NS
	C_{max}	3.94	(0.60)	4.21	(0.59)	NS
CIP 2	$t_{1/2el}$	3.4	(0.9)	3.9	(1.0)	$p<0.05$
	AUC	22.4	(7.5)	35.2	(18.7)	$p<0.01$
	t_{max}	0.71	(0.26)	1.04	(0.75)	NS
	C_{max}	4.49	(1.29)	4.88	(0.81)	NS
CIP 3	$t_{1/2el}$	3.4	(1.0)	4.3	(1.2)	$p<0.01$
	AUC	20.4	(6.8)	32.2	(13.6)	$p<0.01$
	t_{max}	0.90	(0.40)	0.90	(0.40)	NS
	C_{max}	3.91	(1.06)	4.57	(0.74)	$p<0.05$
ENX 1	$t_{1/2el}$	3.0	(1.1)	6.1	(1.7)	$p<0.01$
	AUC	20.0	(7.8)	47.6	(17.2)	$p<0.001$
	t_{max}	0.80	(0.30)	1.00	(0.60)	NS
	C_{max}	3.99	(0.80)	5.00	(1.14)	$p<0.05$
ENX 2	$t_{1/2el}$	3.4	(1.2)	7.7	(2.5)	$p<0.001$
	AUC	21.8	(8.7)	60.2	(15.4)	$p<0.001$
	t_{max}	1.00	(0.50)	1.00	(0.50)	NS
	C_{max}	4.27	(0.62)	5.15	(1.00)	$p<0.01$
ENX 3	$t_{1/2el}$	3.3	(1.3)	11.8	(5.0)	$p<0.001$
	AUC	22.6	(9.8)	100.8	(31.5)	$p<0.001$
	t_{max}	0.70	(0.30)	1.10	(0.70)	NS
	C_{max}	3.90	(0.70)	5.51	(1.04)	$p<0.001$

^a $t_{1/2el}$ (h), AUC ($\text{mg}\cdot\text{h}\cdot\text{l}^{-1}$) dose-normalized, t_{max} (h), C_{max} (mg/l)

Chemical Analyses

Caffeine and paraxanthine concentrations were simultaneously determined by HPLC [34]. The detection limit for both substances was 0.2 mg/l, and the detection range was linear up to 20 mg/l.

Pharmacokinetic Calculations

1. Caffeine

t_{max} and C_{max} were derived from the plasma concentration-time curves. $t_{1/2el}$ was calculated from those curves using a one compartment open model,

Table 4. Mean (SD) kinetic parameters of Paraxanthine alone and during treatment with quinolone antibiotics ($n=12$; Wilcoxon matched pairs sign rank test)

Parameter ^a		Alone		During		
		x	(SD)	x	(SD)	
OFL	$t_{1/2el}$	3.0	(1.2)	2.8	(1.2)	NS
	AUC	16.0	(5.2)	15.2	(6.0)	NS
	t_{max}	5.70	(1.89)	4.32	(0.94)	$p < 0.05$
	C_{max}	1.17	(0.22)	1.11	(0.16)	NS
NOR	$t_{1/2el}$	2.8	(1.3)	3.4	(1.3)	NS
	AUC	23.8	(9.0)	26.4	(13.6)	NS
	t_{max}	4.70	(2.10)	6.00	(3.20)	NS
	C_{max}	1.56	(0.45)	1.50	(0.39)	NS
PPA	$t_{1/2el}$	2.7	(1.2)	9.6	(5.3)	$p < 0.001$
	AUC	22.0	(6.7)	43.0	(15.9)	$p < 0.001$
	t_{max}	4.80	(2.20)	14.40	(5.60)	$p < 0.01$
	C_{max}	1.60	(0.32)	1.28	(0.26)	$p < 0.001$
CIP 1	$t_{1/2el}$	2.6	(1.4)	3.3	(1.7)	$p < 0.05$
	AUC	26.6	(7.5)	23.0	(8.9)	NS
	t_{max}	5.70	(2.90)	6.50	(3.30)	$p < 0.05$
	C_{max}	1.57	(0.33)	1.48	(0.31)	NS
CIP 2	$t_{1/2el}$	3.0	(1.0)	4.1	(1.8)	$p < 0.05$
	AUC	18.5	(7.8)	20.2	(4.7)	$p < 0.05$
	t_{max}	5.30	(2.90)	7.09	(2.34)	$p < 0.05$
	C_{max}	1.15	(0.19)	1.19	(0.23)	NS
CIP 3	$t_{1/2el}$	2.6	(0.9)	4.4	(1.3)	$p < 0.001$
	AUC	20.2	(8.3)	26.6	(11.3)	$p < 0.05$
	t_{max}	4.30	(1.40)	7.70	(3.10)	$p < 0.05$
	C_{max}	1.38	(0.35)	1.33	(0.34)	NS
ENX 1	$t_{1/2el}$	2.6	(1.2)	4.7	(1.8)	$p < 0.05$
	AUC	22.7	(8.5)	32.4	(9.9)	$p < 0.01$
	t_{max}	5.50	(2.60)	9.90	(3.60)	$p < 0.01$
	C_{max}	1.57	(0.27)	1.33	(0.22)	NS
ENX 2	$t_{1/2el}$	3.1	(1.4)	7.9	(3.9)	$p < 0.01$
	AUC	21.9	(5.8)	39.2	(9.1)	$p < 0.01$
	t_{max}	5.30	(2.60)	12.60	(4.70)	$p < 0.01$
	C_{max}	1.57	(0.30)	1.24	(0.27)	$p < 0.05$
ENX 3	$t_{1/2el}$	2.7	(1.1)	14.3	(20.8)	$p < 0.05$
	AUC	22.6	(9.8)	100.8	(31.5)	$p < 0.001$
	t_{max}	5.15	(1.55)	20.73	(6.03)	$p < 0.001$
	C_{max}	1.23	(0.22)	1.35	(0.53)	NS

^a $t_{1/2el}$ (h), AUC ($\text{mg} \cdot \text{h} \cdot \text{l}^{-1}$) dose-normalized, both calculated with TOPFIT; t_{max} (h), C_{max} (mg/l)

AUC, calculated using the trapezoidal rule, was extrapolated and dose-normalized to 3.0 mg/kg.

2. Paraxanthine

t_{max} and C_{max} were derived from the plasma concentration-time curves. $t_{1/2el}$ and AUC (dose-normalized to 3.0 mg/kg) were calculated from the plasma concentration-time curves using the pharmacokinetic software TOPFIT [5].

Statistical analysis (intraindividual comparison of the pharmacokinetic parameters before and during quinolone administration) employed the WILCOXON matched-pairs sign rank test.

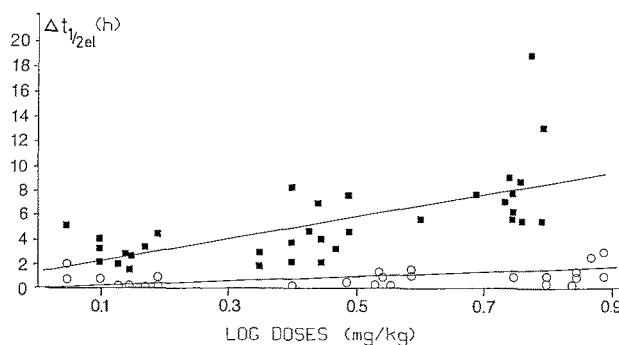


Fig. 1. Correlation between doses of enoxacin (■) and ciprofloxacin (○) and the resulting effect on caffeine elimination expressed as $\Delta t_{1/2el}$ (h) during and before quinolone ($f(x)$); each regression line is formed by 36 data-pairs:

$$f(x)_{ENX} = 1.39 + 9.2 x, \quad r = 0.67, \quad p < 0.001$$

$$f(x)_{CIP} = 0.02 + 1.11 x, \quad r = 0.35, \quad p < 0.05$$

The dose-dependency of effects after enoxacin and ciprofloxacin were calculated by correlation analysis (PEARSON). Data pairs comprised the individual quinolone dose (log dose in mg/kg) and the difference between the caffeine elimination half life before and during quinolone in each volunteer.

Results

The t_{max} , C_{max} , $t_{1/2el}$, and AUC of caffeine and paraxanthine are shown in Tables 3 and 4.

Pipemidic acid and enoxacin had a marked inhibitory effect on caffeine and paraxanthine elimination.

Even at the lowest dose (100 mg b.d.) enoxacin caused as much as a two-fold increase in the elimination half-life of caffeine and paraxanthine.

Ciprofloxacin had a small but significant effect on the elimination of caffeine and paraxanthine in doses exceeding 250 mg b.d.; 100 mg b.d. led only to a slight increase in t_{max} and $t_{1/2el}$ of paraxanthine. The highest dose of ciprofloxacin used (500 mg b.d.) lead to prolongation of the elimination of caffeine and paraxanthine of 1.3-fold and 1.7-fold, respectively.

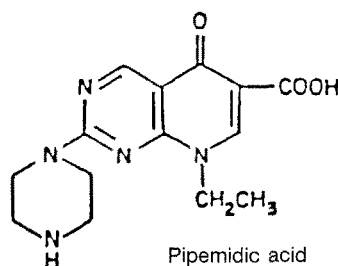
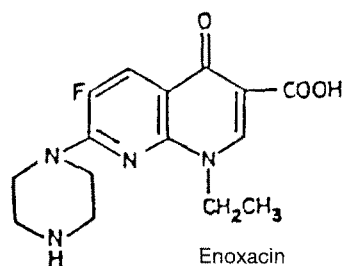
Norfloxacin 400 mg b.d. showed a slight effect, apparent as a small but significant 1.2-fold prolongation in the caffeine elimination half-life.

Ofloxacin (200 mg b.d.) did not prolong the elimination of caffeine and paraxanthine.

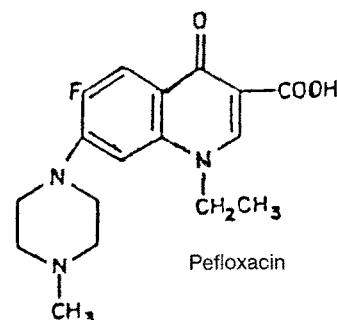
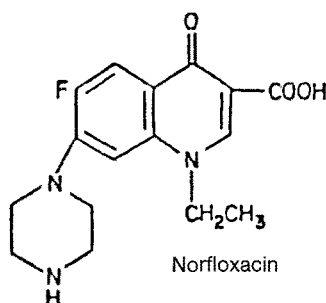
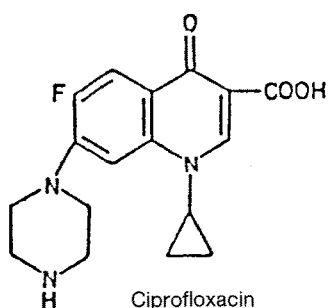
The pharmacokinetic parameters of caffeine and paraxanthine derived from the plasma concentration-time curves before administration of the quinolones were in the normal range and agreed with published results [17, 18].

The correlation between the different dosages of enoxacin and ciprofloxacin and the resulting effects expressed as the difference between the elimination

marked inhibitory effect on methylxanthine elimination



slight inhibitory effect on methylxanthine elimination



no inhibitory effect on methylxanthine elimination

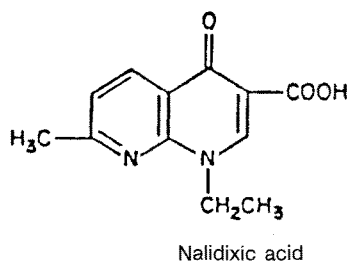
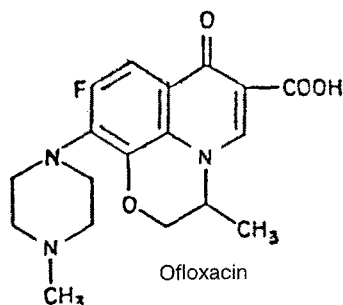


Fig. 2. Molecular structures of the 4-quinolones

half-life of caffeine before and after these doses is shown in Fig. 1. There was a positive correlation for enoxacin and ciprofloxacin, even though the latter led to a smaller increase in the half-life.

Discussion

The results of the first study have previously been published [29, 30], and the findings for ciprofloxacin have been confirmed by others (Healy et al. 1987, unpublished data).

The present study has given further evidence of the inhibitory action of enoxacin on xenobiotic biotransformation. In addition to the findings with

theophylline [2, 32, 33], an influence on antipyrine metabolism (Logemann and Ohnhaus 1986, unpublished data) and on certain P-450 isoenzymes (7-ethoxycoumarin-O-deethylase, benzphetamine-N-demethylase and aniline hydroxylase; [26]) has already been described. The results demonstrate that the inhibition of caffeine elimination (Table 3) is due to a delay in formation of paraxanthine (expressed as prolongation of t_{\max} of this main metabolite), indicating interaction with the 3-demethylation step, which accounts for 80% of caffeine degradation in man [1]. The catabolism of paraxanthine by demethylation and hydroxylation was also inhibited (expressed as prolongation of the half-life of paraxanthine and as an increase in its AUC; Table 4).

Theophylline metabolism, mainly hydroxylation, is also inhibited by enoxacin. Although a decrease in the renal clearance of theophylline metabolites after enoxacin has been discussed by Beckmann et al. [2], saturation of methylxanthine metabolism caused by cumulation of metabolites would not be expected.

Thus, it appears that at least two important pathways of xenobiotic biotransformation, N-demethylation and hydroxylation, are affected by enoxacin and pipemidic acid.

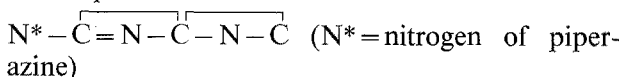
Although the results point to a dose-related effect on caffeine biotransformation, the mechanism of the inhibition is not known, as in vitro data have not been published. It should be noticed that pipemidic acid is not further metabolized by the human liver [16], so it may not compete directly with caffeine in catabolic pathways.

Wijnands et al. [33] concluded that the degree of inhibitory effect on theophylline elimination was correlated with the amount of 4-oxo-metabolite produced from the various quinolones; enoxacin, with a high level of 4-oxo-metabolite (12%–14%), had a marked inhibitory effect, ciprofloxacin, with a small amount of 4-oxo-metabolite (5%–7%), had a moderate effect, and nalidixic acid and ofloxacin, with no or negligible metabolism, had no apparent effect.

However, pipemidic acid, which does not form a 4-oxo-metabolite [16], had a strong inhibitory effect. Furthermore, pefloxacin forms only traces of a 4-oxo-metabolite [23], but shows a moderate inhibitory effect on theophylline elimination, comparable to that of ciprofloxacin [33].

An alternative hypothesis involves a structure-effect relationship. Strong interactive potency is coincident with the *naphthyridine* (enoxacin) or *pyrido-pyrimidine* structure (pipemidic acid) bound to a piperazine ring (Fig. 2).

The sequence



appears essential for a marked inhibitory action.

Low inhibitory activity is found in genuine *quinolone* derivatives (ciprofloxacin, norfloxacin) with a piperazine ring. In the latter case, the lower inhibitory potency could be attributed to deviation from this structure, but with maintenance of a similar spatial structure with decreased affinity for the cytochrome P-450 isoenzyme.

No inhibitory effect was seen with the *pyridobenzoxacin* derivative ofloxacin, where an additional ring formed with an oxo-group radically changes the spatial structure of the compound, nor

with nalidixic acid, where the absence of the *piperazine* ring leads to an inactive compound, as demonstrated by Wijnands et al. [33] for interaction with theophylline.

A structure-effect relationship with the naphthyridine moiety alone was discussed by Niki et al. [21], but the lack of effect of nalidixic acid was not considered.

The present hypothesis is supported by the fact that pefloxacin has a quinolone-structure comparable to that of ciprofloxacin and because nalidixic acid lacks a piperazine substituent. Investigations in vitro, e.g. with human liver microsomes or cytochrome P450-binding studies, are required to prove the hypothesis.

Inhibition of methylxanthine metabolism is known to occur with cimetidine, mexitilene [14], erythromycin, chloramphenicol and other compounds. Investigation of the inhibition by chloramphenicol of the metabolism of theophylline [7], phenytoin [15] and coumarin [9] support the conclusion that drugs which lead to inhibition of cytochrome P450-dependent caffeine metabolism may also inhibit the elimination of other drugs metabolized by cytochrome P450.

The finding of an inhibitory effect of enoxacin and pipemidic acid can possibly be extrapolated to other substances which are clinically more important than caffeine. There is, for example, a need for special caution when these antibiotics are used in patients with hepatic disorders in whom liver metabolism is already compromised. Concerning the slight effect of ciprofloxacin on caffeine biotransformation it should be noticed, that Bem et al. [3], Nix et al. [23] and Schwartz et al. [28] have demonstrated that the inhibitory action of ciprofloxacin ought not to be neglected, as a dose of 750 mg b.d. leads to about a 50% delay in the elimination of methylxanthines. In drugs with a small therapeutic range this could cause severe cumulation, as already described for theophylline [3, 25].

Minor side-effects of caffeine, such as insomnia and restlessness, occur at plasma concentrations above 5 to 10 mg/l. Higher levels may cause seizures and cardiac arrhythmias [24, 27]. Some of the side-effects attributed to enoxacin and pipemidic acid might be due to sustained caffeine levels, which could result from normal caffeine consumption. The dose of caffeine used here (230 mg) is equivalent to 3 or 4 cups of coffee, and the C_{\max} of caffeine after enoxacin and pipemidic acid was about 5 mg/l. It would be prudent to restrict caffeine intake during systemic therapy with enoxacin and pipemidic acid, especially in patients with epileptic seizures or hepatic dysfunction.

CNS-related side-effects have been reported during medication with ofloxacin, which has no effect on methylxanthine elimination. This could be due to the fact that, in comparison with the other 4-quinolones, ofloxacin shows a higher degree of CNS-penetration [20, 26] and may have an affinity for neuronal receptors sites [31].

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