Eur J Clin Pharmacol (1988) 35: 651–656

European Journal of Clinical Pharmacology

4-Quinolones Inhibit Biotransformation of Caffeine

S. Harder[1], A. H. Staib[1], C. Beer[1], A. Papenburg[1], W. Stille[2], and P. M. Shah[2]

Departments of [1] Clinical Pharmacology and [2] Infectious Diseases, University Hospital, Frankfurt/Main, Federal Republic of Germany

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-benzoxacine 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 theophylline 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 ($mg \cdot h \cdot l^{-1}$) 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 ($mg \cdot h \cdot l^{-1}$) 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.

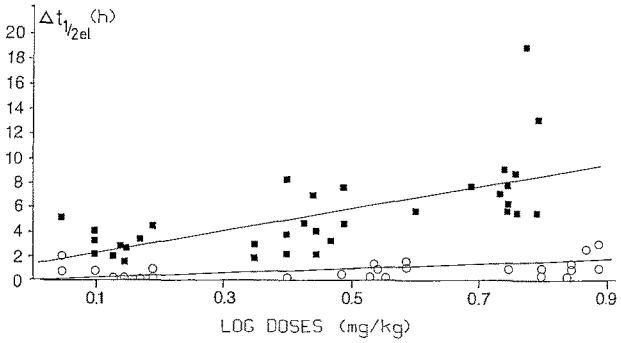

Fig. 1. Correlation between doses of enoxacin (■) and ciprofloxacin (○) and the resulting effect on caffeine elimination expressed as Δ $t_{1/2el}$ (h) during and before quinolone (f(x)); each regression line is formed by 36 data-pairs:
$f(x)_{ENX} = 1.39 + 9.2\ x$, $r=0.67$, $p<0.001$
$f(x)_{CIP} = 0.02 + 1.11\ x$, $r=0.35$, $p<0.05$

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

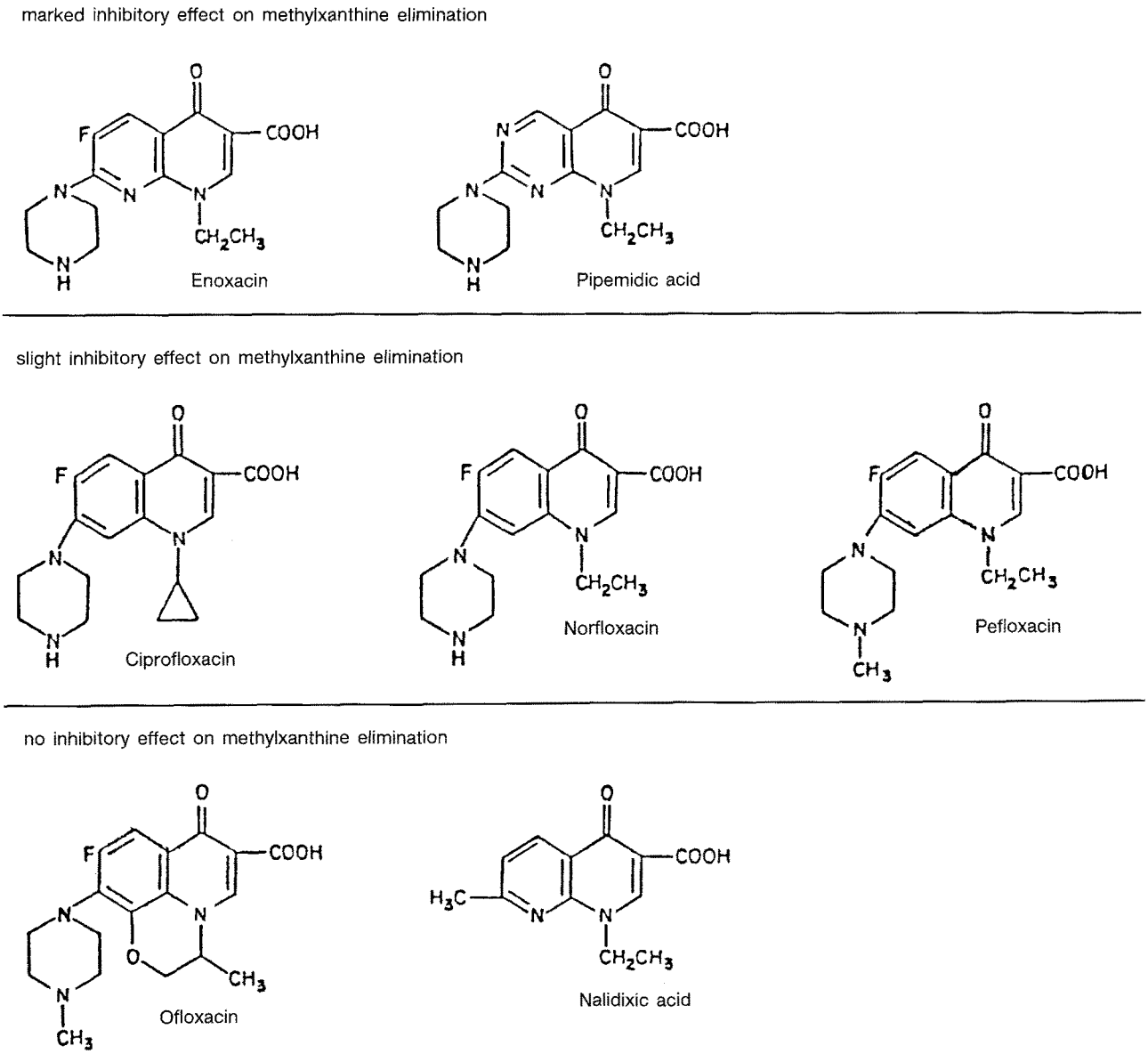

Fig. 2. Molecular structures of the 4-quinolones

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

$N^* - \overline{C = N - C} \overline{- N - C}$ (N^* = nitrogen of piperazine)

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 *pyrido-benzoxacin* 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].

References

1. Arnaud MJ (1984) Products of metabolism of caffeine. In: Dews PB (ed) Caffeine. Springer, Berlin Heidelberg New York Tokyo, pp 3–47
2. Beckmann J, Elsäßer W, Gundert-Remy U, Hertrampf R (1987) Enoxacin – a potent inhibitor of theophylline metabolism. Eur J Clin Pharmacol 33: 227–230
3. Bem JL, Mann RD (1988) Danger of interaction between ciprofloxacin and theophylline. Br Med J 296: 1131
4. Bonati M, Garattini S (1984) Interspecies comparison of caffeine disposition. In: Dews PB (ed) Caffeine. Springer, Berlin Heidelberg New York Tokyo, pp 48–56
5. Bozler G, van Rossum J (1982) Data analysis and evaluation techniques during drug development. G. Fischer, Stuttgart New York, p 207
6. Broughton LJ, Rogers HJ (1981) Decreased systemic clearance of caffeine due to cimetidine. Br J Clin Pharmacol 12: 103–108
7. Busby M, Lesko LJ (1987) Pharmacokinetic interaction between theophylline and chloramphenicol in rats. Drug Metab Dispos 15: 204–206
8. Campbell ME, Grant DM, Inaba T, Kalow W (1987) Biotransformation of caffeine, paraxanthine, theophylline, and theobromine by polycyclic aromatic hydrocarbon-inducible cytochrome P-450 in human liver microsomes. Drug Metabol Disp 15: 237–249
9. Christensen LK, Skovsted L (1969) Inhibition of drug metabolism by chloramphenicol. Lancet 2: 1397–1399
10. Dews PB (1984) Behavioral effects of caffeine. In: Dews PB (ed) Caffeine. Springer, Berlin Heidelberg New York Tokyo, pp 86–103
11. Fourtillan JB, Granier J, Saint-Salvi B, Salmon J, Surjus A, Tremblay D, Vincent Du Laurier M, Beck M (1986) Pharmacokinetics of ofloxacin and theophylline alone and in combination. Infection 14 [Suppl 1]: 67–69
12. Gregoire SL, Grasela TH, Freer JP, Tack KJ, Schentag JJ (1987) Inhibition of theophylline clearance by coadministered ofloxacin without alteration of theophylline effects. Antimicrob Agents Chemother 31: 375–378
13. Janknegt R (1986) Fluorinated quinolones. A review of their mode of action, pharmacokinetics and clinical efficacy. Pharm Weekbl (Sci) 8: 1–21
14. Joeres R, Richter E (1987) Mexitilene and caffeine elimination. N Engl J Med 317: 117
15. Koup JR, Gibaldi M, McNamara P, Hilligoss DM, Colburn WA, Bruck E (1978) Interaction of chloramphenicol with phenytoin and phenobarbital. Clin Pharmacol Ther 24: 571–575
16. Kurobe N, Nakamura S, Shimizu M (1980) Metabolites of pipemidic acid in human urine. Xenobiotica 10: 7–46
17. Lelo A, Birkett DJ, Robson RA, Miners JO (1986) Comparative pharmacokinetics of caffeine and its primary demethylated metabolites paraxanthine, theobromine and theophylline in man. Br J Clin Pharmacol 22: 77–82
18. Lelo A, Miners JO, Robson RA, Birkett DJ (1986) Quantitative assessment of caffeine partial clearances in man. Br J Clin Pharmacol 22: 183–186
19. Maesen FPV, Teengs JP, Baur C, Davies BI (1984) Quinolones and raised plasma concentrations of theophylline. Lancet 2: 530
20. Neuman M (1988) Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin Pharmacokinet 14: 96–121
21. Niki Y, Soejima R, Kawane H, Sumi M, Umeki S (1987) New synthetic quinolone antibacterial agents and serum concentration of theophylline. Chest 92: 663–669
22. Nix DE, DeVito JM, Whitbread MA, Schentag JJ (1987) Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. J Antimicrob Chemother 19: 263–269
23. Nix DE, Schentag JJ (1988) The quinolones. An overview and comparative appraisal of their pharmacokinetics and pharmacodynamics. J Clin Pharmacol 28: 169–178
24. Rall TW (1987) The xanthines. In: Goodman LS, Gilman GA, Rall TW, Murad F (eds) The pharmacological basis of therapeutics. MacMillan, New York, p 592
25. Raoof S, Wollschläger C, Khan F (1985) Serum theophylline levels are increased by ciprofloxacin (BAY 9867), a new quinolone antibiotic. Chest 88: 32 (S)
26. Rietbrock N, Staib AH (1987) Gyrase-Hemmer: Unerwünschte zentralnervöse Wirkungen. Dtsch Med Wschr 112: 201
27. Robertson D, Curatolo PW (1984) The cardiovascular effects of caffeine. In: Dews PB (ed) Caffeine. Springer, Berlin Heidelberg New York Tokyo, pp 77–85
28. Schwartz J, Jauregui L, Lettieri J, Bachmann K (1988) Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. Antimicrob Agents Chemother 32: 75–77
29. Staib AH, Harder S, Mieke S, Beer C, Stille W, Shah PM, Frech K (1986) Gyrase-Hemmer können die Coffein-Elimination verzögern. Dtsch Med Wschr 111: 1500
30. Stille W, Harder S, Mieke S, Beer C, Shah PM, Frech K, Staib AH (1987) Decrease of caffeine elimination in man during co-administration of 4-quinolones. J Antimicrob Chemother 20: 729–734
31. Tsuji A, Sato H, Kume Y, Tamai I, Okezaki E, Nagata O, Kato H (1988) Inhibitory effects of quinolone antibacterial agents on y-aminobutyric acid binding to receptor sites in rat brain membranes. Antimicrob Agents Chemother 32: 190–194
32. Wijnands WJA, van Herwaarden CLA, Vree TB (1984) Enoxacin raises plasma theophylline concentrations. Lancet 1: 108–109
33. Wijnands WJA, Vree TB, van Herwaarden CLA (1986) The influence of quinolone derivatives on theophylline clearance. Br J Clin Pharmacol 22: 677–683
34. Zilly W, Caesar U, Staib AH, Heusler H, Richter E (1982) Die Elimination von Coffein bei Lebererkrankungen. In: Rietbrock N, Woodcock BG, Staib AH (eds) Methods in clinical pharmacology III: Theophylline and other methylxanthines. Vieweg, Braunschweig Wiesbaden, pp 69–75

Received: March 31, 1988
accepted in revised form: July 14, 1988

Prof. Dr. A. H. Staib
Abteilung Klinische Pharmakologie, Klinikum der
Johann Wolfgang Goethe-Universität Frankfurt
Theodor-Stern-Kai 7
D-6000 Frankfurt/Main 70
Federal Republic of Germany