Ciprofloxacin-Caffeine: A Drug Interaction Established Using *In Vivo* and *In Vitro* Investigations

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The inhibitory effects of ciprofloxacin and other quinolone derivatives on the hepatic cytochrome P450-dependent metabolism of caffeine have been investigated in humans. *In vivo* studies involved an intraindividual comparison of the single-dose kinetics of caffeine before and during quinolone administration in 12 healthy men. Changes of enzymatic caffeine degradation by the quinolones were studied *in vitro* using human liver microsomes from three donors. Enoxacin and pipemidic acid markedly prolonged caffeine elimination *in vivo*. A positive correlation exists between the doses of enoxacin or ciprofloxacin and the prolongation (increases) in the caffeine elimination half-life. Decreases in caffeine elimination, using doses of ciprofloxacin in the upper part of the recommended dose range, were approximately 1.5-fold in comparison with untreated control subjects, whereas in the case of enoxacin there was a sixfold change. *In vitro* results with enoxacin, ofloxacin, ciprofloxacin, and pipemidic acid show a competitive inhibition (Dixon plots) of caffeine 3-demethylation. Ciprofloxacin and enoxacin showed the strongest inhibitory effects *in vitro*, whereas ofloxacin had the lowest inhibitory effect. These results are qualitatively reflected in the *in vivo* results; however, the clinical effects may be dependent on pharmacokinetic disposition of the quinolone and this could explain the weak inhibitory action of ciprofloxacin *in vivo*.

Several quinolone derivatives are known to inhibit methylxanthine elimination in humans. Although this interaction has clinical importance primarily in the case of theophylline and enoxacin [1–4], inhibition of theophylline and caffeine metabolism to various extents is also described for pipemidic acid [5–7], pefloxacin [5,8], norfloxacin [3,5–7], and ciprofloxacin [6–13]. The mechanism of the inhibitory action on the hepatic cytochrome P450-dependent methylxanthine metabolism is not yet clearly defined [7,14]. *In vitro* investigations with human liver microsomes are suitable for characterization of the interactive effects of quinolones on the kinetics of methylxanthine enzymatic degradation [14,15]. The following *in vivo* and *in vitro* studies with caffeine (1,3,7-trimethylxanthine) characterize the interactive potency of ciprofloxacin and enable a comparison to be made with other quinolone antibacterials.

MATERIALS AND METHODS

In vivo studies with human volunteers were used to evaluate the effect of enoxacin, ciprofloxacin, pipemidic acid, ofloxacin, and norfloxacin on caffeine elimination [7]. Ciprofloxacin and enoxacin were administered at three different dose levels and the dose range included commonly used therapy (**Table I**). In addition, the influence of enoxacin, ciprofloxacin, pipemidic acid, and ofloxacin on caffeine demethylation in human liver microsomes from three donors (**Table II**) was also conducted.

RESULTS

In vivo results showed a marked inhibitory effect of enoxacin and pipemidic acid on the elimination kinet-

TABLE I

***In Vivo* Investigations of the Influence of Different Doses of Cirpofloxacin and other Quinolones on the Single-Dose Kinetics of Caffeine Investigated in 12 Healthy Men 20 to 40 Years of Age**

Day 1 (morning)
230 mg caffeine administered orally
Plasma samples taken over 24 hours (0, 0.5, 1, 2.4, 6, 8, 12, 16, 24 hours)
Day 2 to Day 4
Quinolone* administration b.i.d.
Day 5 (morning)
230 mg caffeine administered orally
Last dose of quinolone given
Plasma samples taken over 24 hours (0, 0.5, 1, 2, 4, 6, 8, 12, 16, 24 hours)

b.i.d. = twice a day.
Quinolone dosage: ofloxacin 200 mg; norfloxacin 400 mg; pipemidic acid 400 mg; ciprofloxacin 100 mg, 250 mg, and 500 mg; enoxacin 100 mg, 200 mg, and 400 mg. Two weeks washout phase, then repetition with the next quinolone in a randomized sequence. Caffeine concentrations in plasma: high-performance liquid chromatography. Elimination half-life of caffeine: one-compartment model. Total body clearance of caffeine: dose/ area under the curve from time zero to infinity. Statistical calculations by Wilcoxon matched pairs sign rank test.

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TABLE II

In Vitro* Investigation: Influence of Quinolones on Caffeine Degradation Investigated in Liver Microsomes from Three Human Donors

NADPH-Regenerating System
+ Substrate: caffeine; concentrations of 0, 125, 250, 500, 750, 1,000, and 2,000 μM
+ Inhibitor: CIP, PPA, OFL, ENX; concentrations of 0, 25, 50, 125, 250, 500, 750, and 1,000 μM
15-minute incubation (Donor 3, 30 minute): measurement of caffeine's major metabolite 1,7-dimethylxanthine by HPLC

NADPH = reduced nicotinamide-adenine dinucleotide phosphate; CIP = ciprofloxacin; PPA = pipemidic acid; OFI = ofloxacin; ENX = enoxacin; HPLC = high-performance liquid chromatography.
*Donors undergoing liver surgery and receiving no drugs known to affect the cytochrome P450 system. Hanes plots: K_m, V_{max}; Dixon plots: type of inhibition, K_i.

TABLE III

Caffeine Elimination Half-Lives after Administration Alone and During Treatment with Quinolone Antibiotics*

Quinolone	Dose† (mg)	Alone Mean ± SD	During Mean ± SD	p Value ‡
Ofloxacin	200	2.9 ± 0.7	2.8 ± 1.0	NS
Norfloxacin	400	3.2 ± 1.1	3.7 ± 1.1	p <0.05
Pipemidic acid	400	3.3 ± 1.1	7.3 ± 3.2	p <0.001
Ciprofloxacin	100	3.4 ± 1.2	3.6 ± 1.5	NS
Ciprofloxacin	250	3.4 ± 0.9	3.9 ± 1.0	p <0.05
Ciprofloxacin	500	3.4 ± 1.0	4.3 ± 1.2	p <0.01
Enoxacin	100	3.0 ± 1.1	6.1 ± 1.7	p <0.01
Enoxacin	200	3.4 ± 1.2	7.7 ± 2.5	p <0.001
Enoxacin	400	3.3 ± 1.3	11.8 ± 5.0	p <0.001

NS = not significant.
*For details see Table I.
†Twice a day.
‡Wilcoxon matched pairs sign rank test; significance level, p >0.05.

TABLE IV

Caffeine Clearance after Administration Alone and during Treatment with Quinolone Antibiotics*

Quinolone	Dose† (mg)	Alone Mean	Alone SD	During Mean	During SD	p Value ‡
Ofloxacin	200	164	70	160	67	NS
Norfloxacin	400	166	68	142	63	NS
Pipemidic acid	400	159	61	56	18	p <0.01
Ciprofloxacin	100	168	91	138	54	p <0.05
Ciprofloxacin	250	143	54	99	32	p <0.01
Ciprofloxacin	500	170	83	111	53	p <0.01
Enoxacin	100	174	73	71	24	p <0.01
Enoxacin	200	157	60	54	17	p <0.01
Enoxacin	400	149	68	32	9	p <0.001

NS = not significant.
*Caffeine clearance is the dose divided by the AUC, in ml/hour/kg. For details see Tables I and III.
†Twice a day.

ics of caffeine by which the elimination half-life was increased and clearance decreased (**Tables III** and **IV**). Even the lowest dose of enoxacin (100 mg twice daily) produced a twofold (averaged) increase in elimination half-life of caffeine.

Ciprofloxacin has only a weak inhibitory action on caffeine elimination, but this was statistically significant and at a dose rate of 1,000 mg/d leads to a 30 percent (averaged) increase of caffeine elimination half-life.

Correlation analysis (Pearson) of the individually given enoxacin and ciprofloxacin doses and the observed prolongation of caffeine elimination half-life gave positive correlations described by the following equations: $f(X)_{enx}$ equals 48 plus 20.2X ($r = 0.729$; $p < 0.001$) for 36 patients and $f(X)_{cip}$ equals −3 plus 3.3X ($r = 0.476$; $p < 0.01$) for 36 patients, where $f(X)_{enx}$ and $f(X)_{cip}$ are the percent change versus untreated control values for doses in mg/kg of enoxacin and ciprofloxacin, respectively. Maximal prolongation of caffeine degradation by ciprofloxacin when given at a dose rate corresponding to the upper part of the recommended dose range (1,500 mg per day) is about 1.5-fold, whereas the inhibition produced by enoxacin, according to the slope of the dose-response curve, is many-fold stronger (**Figure 1**). The mean elimination half-life of caffeine before application of enoxacin and ciprofloxacin, however, was 3.3 hours with a coefficient of variation of 33 percent, and there was an overlap in the control and serum half-lives using ciprofloxacin at low doses.

The inhibitory effects of the quinolones on caffeine 3-demethylation *in vitro* are demonstrated by comparison of the apparent Michaelis-Menten constant (K_m) of caffeine and the inhibitory rate constant (K_I) (**Table V**). Similar maximal formation rates with and without inhibitor (Dixon plots) show that the inhibitory effects of ciprofloxacin on caffeine 3-demethylation is of the competitive type at a common binding site (e.g., donor 2, **Figure 2**).

K_I values for enoxacin and ciprofloxacin are much below the K_m for caffeine, indicating a high affinity to the caffeine binding site for demethylation. On the other hand, the K_I of ofloxacin indicates only a weak affinity to the binding site.

COMMENTS

In vivo results with caffeine support earlier observations of others demonstrating that enoxacin, in particular, leads to clinically important accumulations of theophylline with serious side effects [2,4]. Although ciprofloxacin had only a weak effect on elimination half-life in these subjects, theophylline intoxication has been reported in patients receiving ciprofloxacin and theophylline [11,13,14], indicating that kinetic measurements in experimental subjects may be limited. Ofloxacin and norfloxacin have little or no effect on caffeine and theophylline elimination when administered at normal dose rates [3,5,8,9,14,16].

The possibility that quinolones can interact with and inhibit cytosolic xanthine oxidase cannot be ruled out [1,14,17]. The unchanged maximal concentration and time to maximal concentration of caffeine suggests that quinolones do not modify the absorption and distribution [14,18].

The inhibitory potency of ciprofloxacin *in vitro* is similar to that for enoxacin and thus similar results *in vivo* would be expected. The inhibitory action of ciprofloxacin *in vivo*, however, is much less than that of enoxacin. If it could be shown that *in vitro* findings predict clinically relevant interactions, then such measurements could be used for testing the effect of newly synthesized quinolones on biotransformation of xenobiotics in general. This is because many of these substances have elimination pathways related to that of caffeine [15].

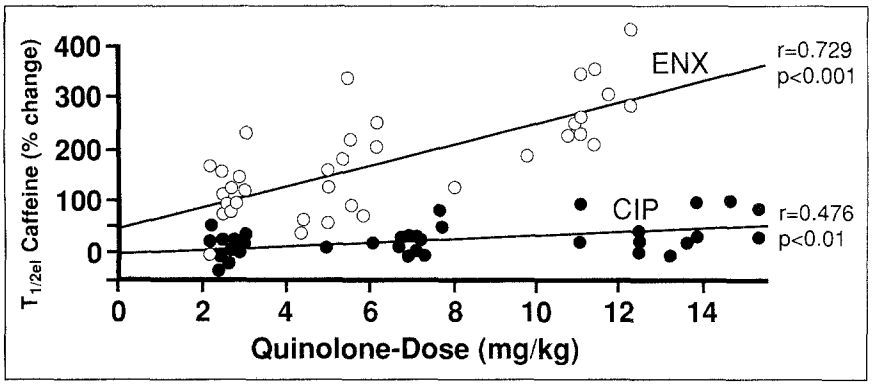

Figure 1. Regression analysis (Pearson) for enoxacin (ENX) and ciprofloxacin (CIP) doses and resulting prolongation of caffeine elimination half-life ($T_{1/2\ el}$) (percent change versus untreated control value).

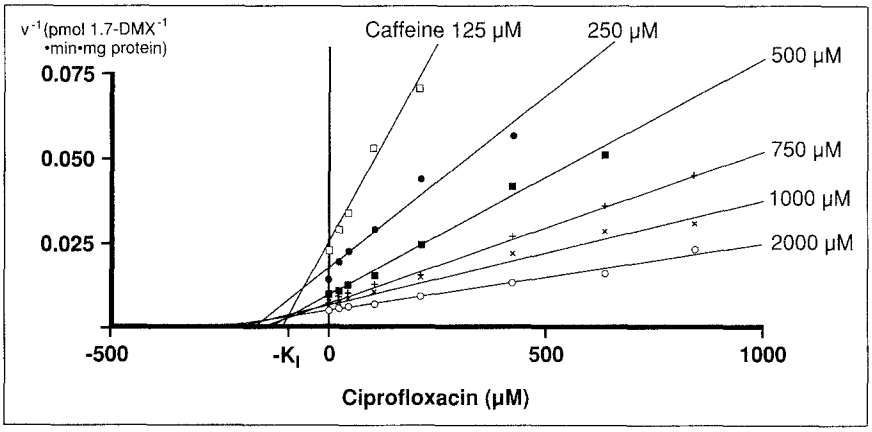

Figure 2. Inhibitory effects of ciprofloxacin on caffeine 3-demethylation by human liver microsomes (donor 2, Dixon plot). DMX = dimethylxanthine.

TABLE V

Apparent Affinity Constants K_m and K_I and Formation Rate (V_{max}) of 1,7-Dimethylxanthine

	V_{max}*	Caffeine K_m (mM)	Ofloxacin K_I (mM)	Pipemidic Acid K_I	Ciprofloxacin K_I	Enoxacin K_I
Donor 1	104	0.58	1.52	0.25	0.09	0.17
Donor 2	241	0.61	5.18	0.29	0.09	0.12
Donor 3	140	1.30	1.60		0.26	0.25

*V_{max} is given in pmol 1,7-dimethylxanthine/minute/mg protein.

Data from the present study suggest that the success of any quinolone treatment using *in vitro* techniques may be limited and mainly reflect only qualitative differences. On the other hand, if K_I values are lower than the K_M of caffeine, an inhibitory action on caffeine (and theophylline) degradation *in vivo* can be expected and appropriate caution should be exercised when using the quinolone in combination with theophylline or drugs having similar biotransformation pathways.

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