Journal of Antimicrobial Chemotherapy (1987) **20**, 729–734

Decrease of caffeine elimination in man during co-administration of 4-quinolones

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The single dose pharmacokinetics of caffeine (220–230 mg per dose) were investigated in 12 healthy male volunteers before and during treatment with ofloxacin (200 mg bd), ciprofloxacin (250 mg bd) and enoxacin (400 mg bd) with a cross-over study design. None of the parameters: mean elimination half-life ($T_{\frac{1}{2}el}$), C_{max}, total body clearance (Cl_{tot}) and the volume of distribution (aV_d) of caffeine were noticeably altered by administration of ofloxacin. Striking changes were observed, however, after administration of enoxacin: the $T_{\frac{1}{2}el}$ was prolonged by as much as 260%, the C_{max} increased by 41%; the aVd was reduced by 20% and Cl_{tot} by 78% (mean values). Treatment with ciprofloxacin led to a prolongation of $T_{\frac{1}{2}el}$ by 15%, to a decrease of aVd by 25% and to a 33% decrease of Cl_{tot}. The results of this intra-individual comparison of caffeine pharmacokinetic data demonstrate that treatment with ciprofloxacin and enoxacin may have a significant inhibitory effect on caffeine elimination.

Introduction

Plasma theophylline levels may be elevated in patients treated simultaneously with enoxacin or ciprofloxacin (Maesen *et al.*, 1984; Wijnands, van Herwaarden & Vree, 1984; Raoof, Wollschläger & Khan, 1985), but not apparently during treatment with ofloxacin (Fourtillan *et al.*, 1986). This interaction is of clinical relevance, for instance in asthmatics with acute bronchitis, or in patients with liver insufficiency (Mangione *et al.*, 1978; Ogilvie, 1978; Staib *et al.*, 1980) as inhibition of theophylline elimination can result in an elevation of theophylline plasma levels beyond the therapeutic range and result in toxicity, features of which include arrhythmias, headache, seizures or other central reactions such as insomnia, restlessness and central agitation (Ogilvie, 1978; Hendeles, Weinberger & Johnson, 1980).

The elimination processes of the related xanthines, caffeine, paraxanthine, and theobromine vary quantitatively (Arnaud, 1984; Lelo *et al.*, 1986*a*) but caffeine kinetics may be affected similarly to those of theophylline, for example, by cirrhosis, congestive heart failure and old age (Zilley *et al.*, 1982; Arnaud, 1984; Joeres *et al.*, 1987) with similar results. Interactions of 4-quinolones with caffeine, contained in beverages and drugs, could be interpreted as side effects of 4-quinolones themselves.

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0305–7453/87/110729+06 $02.00/0

No substantive reports are available on the potential effect of quinolones on caffeine pharmacokinetics, and the present study has been designed to assess such a possible interaction.

Methods

The single dose kinetics of caffeine were investigated in 12 male volunteers aged 24–39 years, one day before and after five days of administration of 4-quinolones, on the basis of intra-individual comparison. Subjects received seven standard doses (day 2 to day 5) of a 4-quinolone, as recommended by the manufacturer: 200 mg bd ofloxacin (Hoechst AG), 250 mg bd ciprofloxacin (Bayer AG), 400 mg bd enoxacin (the commercially available Japanese product Flumark, Dai Nippon Pharmaceuticals Seiyaku, Osaka), in a cross-over design. A single oral dose of a caffeine-citrate solution (220–230 mg caffeine base per dose, i.e. an equivalent to 3–4 cups of coffee) was given on day 1 (before 4-quinolone treatment), and on day 5 (together with the last dose of the 4-quinolone). Subjects were maintained on a methylxanthine-free diet for 36 h before and 24 h after caffeine administration. Each run was followed by a two-week wash out phase, before evaluation of the next 4-quinolone.

Serum-caffeine concentrations were determined by HPLC. Pharmacokinetic parameters were derived from the plasma-concentration/time-curve (C_{max}; T_{max}; $T_{\frac{1}{2}el}$ from the regression-line of the terminal slope; $aV_d = \text{dose}/C_o$; $Cl_{tot} = aV_d \cdot k_{el}$; $AUC_{o\to\infty}$ calculated by the trapezoidal rule with extrapolation to ∞ by C_n/k_{el}). Statistical analysis was performed by the Wilcoxon matched pairs signed rank test for intra-individual comparison (significance limit: $P \leqslant 5\%$).

Table I. Intraindividual comparison of C_{max} (mg/l) and T_{max} (h) of caffeine in adults before (I) and after (II) treatment with ofloxacin, ciprofloxacin and enoxacin[a]

	Ofloxacin				Ciprofloxacin				Enoxacin			
	C_{max}		T_{max}		C_{max}		T_{max}		C_{max}		T_{max}	
Code	I	II	I	II	I	II	I	II	I	II	I	II
A	3·61	4·74	1·0	0·5	4·83	5·47	0·5	1·0	4·30	5·08	0·6	1·3
B	3·34	4·18	0·5	0·5	4·22	3·90	0·5	0·5	3·42	3·84	0·5	1·0
C	5·81	6·45	0·5	0·5	5·31	6·43	0·5	0·5	3·58	6·69	1·0	0·5
E	4·45	4·02	1·0	0·5	3·53	5·03	1·0	0·5	3·42	4·49	1·0	1·0
F	4·21	3·91	2·0	1·0	4·84	5·47	1·0	3·0	4·97	5·52	0·5	1·0
G	5·81	5·95	0·5	1·0	6·69	5·26	1·0	0·5	5·44	6·40	0·5	0·5
H	3·63	3·43	1·0	0·5	3·19	3·97	1·0	0·5	3·69	7·14	1·0	0·5
I	3·75	4·61	0·5	1·1	3·62	4·13	1·0	1·0	3·18	5·36	1·0	2·0
K	3·59	2·35	0·5	0·5	3·31	3·74	0·5	1·0	3·75	6·80	1·0	3·0
L	3·51	4·32	1·0	0·5	3·73	4·66	0·5	1·0	3·61	4·57	0·5	2·0
M	3·47	4·45	1·0	0·5	6·98	5·10	0·5	2·0	4·13	4·93	0·5	0·5
N	3·92	3·61	0·5	0·5	3·58	5·34	0·5	1·0	3·28	5·34	0·5	0·5
χ	4·09	4·34	0·8	0·7	4·49	4·88	0·7	1·0	3·90	5·51	0·7	1·2
S.D.	0·86	1·08	0·4	0·3	1·29	0·81	0·3	0·7	0·70	1·04	0·3	0·8

[a]For the order of administration of the quinolones see Table II.

Statistical results of intra-individual comparison C_{max} caffeine (mg/l) before/after treatment: ofloxacin, n.s.; ciprofloxacin, n.s.; enoxacin, $P < 0{\cdot}001$.

Statistical results of intra-individual comparison T_{max} caffeine (h) before/after treatment: ofloxacin, n.s.; ciprofloxacin, n.s.; enoxacin, n.s.

Results

The observed and derived kinetic data obtained in 12 subjects are documented in Tables I to III. The tables contain the statistical values of the intra-individual comparison of the data before and after treatment. Significant changes in pharmacokinetic parameters of caffeine resulted in subjects treated with enoxacin and ciprofloxacin.

Discussion

The pharmacokinetic parameters of caffeine obtained before 4-quinolone administration were consistent with the results of other investigators (Zilly *et al.*, 1982; Bonati & Garattini, 1894; Joeres *et al.*, 1987; Lelo *et al.*, 1986*a*, 1986*b*). In contrast there was a marked prolongation of the caffeine elimination half-life during co-administration of enoxacin, a moderate prolongation with ciprofloxacin, but only a minimal influence or none with ofloxacin as in preliminary reports (Staib *et al.*, 1986).

This extended study allows the following conclusions. Co-administration of enoxacin 400 mg bd causes up to a five-fold prolongation of the elimination half-life of caffeine. Ciprofloxacin in a dose of 250 mg bd a lesser, but statistically significant, inhibitory effect on caffeine elimination (parameters: $T_{\frac{1}{2}el}$, Cl_{tot}, AUC, aV_d) in healthy adults. The results obtained with ofloxacin are within the normal variability of caffeine kinetics. The lack of effect of co-administration of ofloxacin on caffeine elimination is

Table II. Intra-individual comparison of the elimination half life (h) and of the V_d (l/kg) of caffeine in adults before (I) and after (II) treatment with ofloxacin, ciprofloxacin and enoxacin*

	Ofloxacin				Ciprofloxacin				Enoxacin			
	$T_{\frac{1}{2}el}$		V_d		$T_{\frac{1}{2}el}$		V_d		$T_{\frac{1}{2}el}$		V_d	
Code	I	II	I	II	I	II	I	II	I	II	I	II
A	2·1	2·7 (1)	0·49	0·55	2·6	3·9 (2)	0·41	0·46	3·1	16·3 (3)	0·56	0·63
B	3·1	2·4 (2)	0·50	0·48	4·8	5·1 (1)	0·69	0·56	4·7	10·4 (3)	0·62	0·47
C	2·7	4·5 (1)	0·64	0·56	3·3	3·1 (2)	0·61	0·44	3·0	10·8 (3)	0·57	0·43
E	3·5	2·2 (2)	0·39	0·44	3·3	3·9 (1)	0·54	0·55	4·1	11·8 (3)	0·78	0·53
F	3·9	3·4 (2)	0·53	0·45	3·9	3·6 (2)	0·49	0·34	6·2	25·1 (3)	0·57	0·58
G	4·0	3·3 (1)	0·47	0·43	4·3	4·6 (3)	0·62	0·50	4·2	13·0 (2)	0·54	0·39
H	2·7	2·2 (3)	0·73	0·70	3·3	4·3 (2)	0·82	0·80	2·5	8·2 (1)	0·60	0·41
I	3·4	2·5 (1)	0·62	0·37	3·8	4·2 (3)	0·68	0·51	3·2	10·4 (2)	0·60	0·43
K	2·4	1·8 (2)	0·67	0·86	2·1	3·7 (3)	0·71	0·58	2·0	7·6 (1)	0·61	0·36
L	2·4	2·4 (3)	0·67	0·58	2·4	2·3 (1)	0·68	0·39	1·8	8·0 (2)	0·43	0·48
M	3·6	4·7 (3)	0·78	0·66	4·5	5·9 (1)	0·77	0·46	3·7	12·9 (2)	0·65	0·56
N	1·6	1·6 (3)	0·65	0·62	2·5	2·5 (1)	0·67	0·48	1·6	7·2 (2)	0·63	0·50
χ	2·9	2·8	0·60	0·56	3·4	3·9	0·69	0·50	3·3	11·8	0·60	0·48
S.D.	0·7	1·0	0·12	0·14	0·9	1·0	0·11	0·12	1·3	5·0	0·08	0·08

*The numbers in brackets indicate the order in which the three quinolones were received by each individual; the means ± S.D. of the caffeine $T_{\frac{1}{2}el}$ (h) *before* the quinolone treatment ('control' value comparison) were for the 1st run = 3·17 ± 0·96, 2nd run = 3·03 ± 0·79, 3rd run = 3·47 ± 1·27.

Statistical results of intra-individual comparison of $T_{\frac{1}{2}el}$ caffeine (h) before/after treatment with quinolones (N = 12): ofloxacin, n.s.; ciprofloxacin, $P < 0·05$; enoxacin, $P < 0·001$.

Statistical results of intra-individual comparison of V_d caffeine (l/kg) before/after: ofloxacin, n.s.; ciprofloxacin, $P < 0·01$; enoxacin, $P < 0·01$.

Table III. Intra-individual comparison of total clearance values (ml/h/kg) and AUC-values[a] (mg/h/l) of caffeine in adults before (I) and after (II) treatment with ofloxacin, ciprofloxacin and enoxacin

	Ofloxacin				Ciprofloxacin				Enoxacin			
	Cl_{tot}		AUC		Cl_{tot}		AUC		Cl_{tot}		AUC	
Code	I	II	I	II	I	II	I	II	I	II	I	II
A	162	142	14·2	18·9	110	82	22·6	32·9	125	27	21·3	109·3
B	112	139	24·1	21·9	100	76	39·9	39·1	92	31	31·3	95·9
C	163	86	18·1	34·0	127	99	23·1	29·1	130	28	20·2	107·5
E	80	136	33·2	18·8	113	97	24·0	30·1	132	31	22·7	81·5
F	96	131	28·0	18·5	89	67	31·7	38·5	64	16	45·5	184·0
G	82	89	36·0	31·3	99	75	31·4	39·1	92	21	31·8	128·0
H	183	220	15·3	12·3	171	128	16·5	22·1	163	35	19·1	79·5
I	127	103	22·1	24·0	125	84	22·8	33·8	130	29	21·0	100·6
K	194	325	13·4	7·6	230	110	11·5	23·3	212	33	12·3	88·0
L	192	164	13·8	16·7	196	118	14·2	21·5	167	42	13·5	71·6
M	151	96	19·7	30·3	120	53	27·9	90·7	122	30	23·1	98·6
N	292	273	9·2	9·7	187	132	11·6	21·9	271	48	9·6	64·9
χ	153	159	20·6	20·3	138	93	22·4	35·2	142	31	22·6	100·8
S.D.	60	76	8·4	8·4	45	25	7·5	18·7	56	8	9·8	31·5

[a]All values dose-normalized to 3 mg/kg; for the order of administration of the quinolones see Table II.

Statistical results of intra-individual comparison of Cl_{tot} caffeine (ml/h/kg) before/after: ofloxacin, n.s.; ciprofloxacin, $P<0{\cdot}001$; enoxacin, $P<0{\cdot}001$.

Statistical results of intra-individual comparison of $AUC_{0\rightarrow\infty}$ caffeine (mg/h/l) before/after: ofloxacin, n.s.; ciprofloxacin, $P<0{\cdot}001$; enoxacin, $P<0{\cdot}001$.

in keeping with reported findings for theophylline (Fourtillan *et al.*, 1986; Wijnands *et al.*, 1986). The decreased total clearance of caffeine and increased C_{max} are in accordance with inhibition of caffeine elimination by enoxacin and, to a lesser extent, ciprofloxacin.

The therapeutic use of 4-quinolones (e.g. enoxacin) in patients with liver disease, undergoing intensive care, with cardiac arrhythmias or with latent epilepsy may result in unexpected effects following caffeine intake due to elevated plasma concentrations. The effects and side effects of caffeine may be similar to those observed with theophylline: e.g. tachyarrhythmia, central agitation and nausea (Eichler, 1976; Robertson & Curatolo, 1984; Dews, 1984; Snyder, 1984). Increase of methylxanthine levels, however, may be difficult to assess in rapid changing pathophysiological states, such as those encountered in severe infections and intensive-care patients.

The effect of varying dosages of the 4-quinolones on caffeine elimination should be further investigated as the doses used in this study do not encompass the full recommended dose ranges of the various 4-quinolones (ofloxacin 200–600 bd), ciprofloxacin 250–750 mg bd, enoxacin 200–400 mg bd). Furthermore the biochemical mechanisms of the inhibitory effect of 4-quinolones on caffeine elimination, e.g. inhibition of the microsomal oxidation in the liver, should be examined with reference to published reports on interactions with other agents, such as antipyrine, which may be affected by these processes (Logemann & Ohnhaus, 1986). Available data suggest that the 4-oxo metabolite of quinolones, rather than the parent drug, inhibits theophylline clearance. The effect of enoxacin, ciprofloxacin and pefloxacin on

theophylline clearance is proportional to the formation of 4-oxo metabolites, whereas ofloxacin is not metabolized by this route (Wijnands, Vree & Van Herwaarden, 1986).

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(*Manuscript accepted 3 June 1987*)