Eur J Clin Pharmacol (1990) 39: 63–69

European Journal of Clinical Pharmacology

Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition

G. Barnett[1]*, J. Segura[2], R. de la Torre[2], and M. Carbó[2]

[1] Division of Cardio-Renal Drug Products Food and Drug Administration, Rockville and
[2] Department of Pharmacology and Toxicology Institut Municipal d' Investigació Mèdica, Barcelona, USA and Spain

Received: July 28, 1989/Accepted in revised form: November 21, 1989

Summary. Quinolone is reported to interact with caffeine, often resulting in an increase both in the plasma half-life and AUC, a decrease in total plasma clearance, and little change in the absorption rate constant and maximum plasma level. These complex changes in the pharmacokinetics of caffeine were analyzed experimentally and from published reports in order to determine the nature of the interaction, which is thought to be due to inhibition of caffeine metabolism by quinolones.

A simple pharmacokinetic model for the caffeine-quinolone interaction was developed, which provides a unified method for evaluation and comparison of the effect of quinolones on the disposition of caffeine.

The model is applicable to other methylxanthines, such as theophylline. The relative potency of the interactions of quinolones with caffeine in humans has been established as enoxacin (100), pipemidic acid (29), ciprofloxacin (11), norfloxacin (9) and ofloxacin (0).

Key words: Caffeine metabolism, quinolones; drug interaction, pharmacokinetics, plasma levels, enoxacin, pipemidic acid, ciprofloxacin, norfloxacin, ofloxacin

Quinolone antimicrobial therapy is an area of current research, due primarily to the development of the new synthetic 6-fluoroquinolone agents (Arcieri et al. 1988; Edwards et al. 1988; Nix and Schentag 1988). There have been numerous reports of drug-drug interactions with the methylxanthines, usually marked by altered plasma methylxanthine levels (Wijnands et al. 1984, 1986; Simpson et al. 1985; San José Valverde et al. 1984; Thompson et al. 1987; Carbó et al. 1988; Staib et al. 1987; Harder et al. 1988; Ho et al. 1988; Nix and Schentag 1988; Nix et al. 1987; Raoof et al. 1985; Sano et al. 1988, 1987; Wijnands et al. 1987; Rogge et al. 1988). Pharmacokinetic findings in those studies have suggested that the alteration in xanthine disposition is not related to changes in distribution or renal elimination of unchanged drug but probably to alterations in metabolic elimination pathways. Due to the widespread use of quinolones (Campoli-Richards et al. 1988; Schaeffer et al. 1987; Ramirez-Ronda et al. 1987; Van der Willigen et al. 1987; Davies et al. 1987; Khan et al. 1983; Holms et al. 1985; Shinzu et al. 1975) clinical precautions are required to cover concomitant ingestion with the methylxanthines, since the latter could manifest both central nervous system and cardiovascular side effects due to elevated plasma levels (Rall 1985).

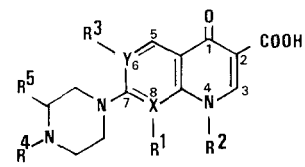
Sufficient data are now available to develop a pharmacokinetic model for the caffeine-quinolone interaction. Two studies (I, II) reported by Carbó et al. (1988) provide a data base for analysis of individual concentration-time (C-t) curves for norfloxacin (NFC) and pipemidic acid (PPA), and for development of a simple pharmacokinetic model for the interaction. A study (III) by Staib et al. (1987) contains data about the interaction with ciprofloxacin (CIP), enoxacin (ENX), and ofloxacin (OFL), which permitted computer simulations with the model describing the interaction of those quinolones with caffeine. The relative potencies of the effects of those five quinolone drugs on the disposition of caffeine in humans are reported here.

Methods

Clinical procedures

Study I. A single dose study of caffeine (C) was carried out in 6 male volunteers, using a 3-way Latin square placebo design to measure the effects of NFC and PPA on the pharmacokinetics of C

* *Present Adress:* Biometric Research Institute, 1401 Wilson Blvd, Suite 400, Arlington, VA 22209, USA



Quinolone	X	Y	R^1	R^2	R^3	R^4	R^5
Pipemidic acid	N	N	-	C_2H_5	-	H	H
Enoxacin	N	C	-	C_2H_5	F	H	H
Norfloxacin	C	C	H	C_2H_5	F	H	H
Ofloxacin	C	C	$-OCH_2CH(CH_3)-$		F	CH_3	H
Ciprofloxacin	C	C	H		F	H	H

Fig. 1. Molecular structures of ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pipemidic acid

(Carbó et al. 1988). In short (see cited reference for further details) the volunteers, all smokers, were restricted to a methylxanthine-free diet. The doses were 350 mg C, 800 mg NFC and 800 mg PPA all administered by the oral route. The protocol design was: on Day 1 volunteers received either placebo or one of the two quinolones every 12 h; on Day 2 they received 1 dose of the same treatment together with 1 dose of C. There was a 7 day washout between treatments. Blood samples were collected predose ($t = 0$) and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 24 h. Samples were analyzed for plasma C concentration.

Study II. A multiple dose study of caffeine was carried out in 2 volunteers, one a smoker (7) and the other a nonsmoker (8), to measure the effect of PPA (Carbó et al. 1988). Volunteer 7 received 100 mg C every 6 h on Days 1 to 5, and he also received 4 doses of 400 mg PPA, every 12 h, on Days 3 and 4. Volunteer 8 received 100 mg C every 8 h on Days 1 to 5 and 3 doses of 400 mg PPA, every 12 h, on Days 3 and 4. Multiple blood samples were collected during the 5 days of the study for analysis of plasma C.

Study III. Staib et al. (1987) reported the effect on C due to treatment with CIP, ENX and OFL. Using a cross-over design they studied 12 males on a methylxanthine-free diet. The doses were 220–230 mg C, 250 mg CIP, 400 mg ENX, and 200 mg OFL, given orally. Blood samples were collected over 24 h, and the plasma concentration of C was determined. The protocol was: on Day 1 each volunteer received 1 dose of C; on Days 2 to 4 they received one of the quinolones as 6 doses on a 12 h schedule; and on Day 5 they received a final dose of quinolone together with 1 dose of C.

Pharmacokinetic analysis

The C-t curves for each volunteer were analyzed by the SAAM/ConSam program (Berman et al. 1978) for least squares fitting to obtain the most accurate representation of the experimental data. The caffeine-only data (placebo condition) was best described by a 1-compartment model with first-order absorption and elimination. The effect of quinolones was best described as an inhibition of caffeine elimination, resulting in nonlinear elimination. Therefore, the pharmacokinetic parameters to describe the model are the absorption rate constant k_{ab}, the elimination rate constant k_{el}, the volume of distribution V, and an inhibition constant k_i for each quinolone drug. The volume of distribution is actually V/f, if complete caffeine absorption is assumed, thus f = 1 (Blanchard et al. 1983). The equations for the rate of change in the plasma caffeine concentration under placebo and treatment conditions are

$$dC/dt = k_{ab}*f*Dose/V - K_{el}*C \text{ (Placebo)} \quad (1)$$

and

$$dC/dt = k_{ab}*f*Dose/V - \frac{k_{el}*C}{(1 + k_i*C)} \text{ (Treatment)} \quad (2)$$

The three C-t curves of caffeine in each volunteer in the single dose study were analyzed simultaneously. Thus, computer estimates of k_{ab}, k_{el} and V utilized information from the 3 curves, while the values of k_i were obtained from the one curve specific to PPA or NFC treatment. For the multidose study the two C-t curves were analyzed, so that the entire curve was utilized to estimate k_{ab}, k_{el} and V, and only the portion of the curve after inhibitor administration was used to estimate k_i for PPA. Weighting experimental data points with a 5% fractional coefficient of variation was found to give optimal estimates of model parameters and sum-of-squares agreement with experimental data for the six single dose and two multiple dose studies.

Computer simulations were carried using the mean data from Staib et al. (1987) to estimate inhibition constants k_i for CIP, ENX and OFL. They reported experimental values for C_{max} and t_{max}, calculated values for $t_{1/2}$ and AUC and estimated values for V and CL_p. In order to obtain values for k_{ab} the t_{max} equation for a 1-compartment model with oral absorption (Gibaldi and Perrier 1985) was solved.

Table 1. Computer estimates of pharmacokinetic parameters of caffeine in subjects treated with placebo (P), pipemidic acid (PPA) and norfloxacin (NFC)

VOL	k_{ab} $l \cdot h^{-1}$	k_{el} $l \cdot h^{-1}$	V l	k_i (ml·μg^{-1})		Sum-of-Squares		
				PPA	NFC	P	PPA	NFC
Single dose study								
1	6.0 (156)	0.183 (3)	56.6 (2)	0.353 (8)	0.0917 (17)	0.38	0.58	0.46
2	3.9 (47)	0.179 (2)	47.6 (2)	0.413 (4)	0.0485 (12)	0.71	0.70	0.53
3	2.0 (10)	0.555 (2)	42.7 (2)	0.594 (3)	0.262 (4)	0.16	0.09	0.02
4	2.0 (12)	0.0615 (6)	45.5 (2)	0.438 (18)	0.0489 (32)	5.88	30.	10.
5	1.9 (9)	0.294 (2)	40.6 (2)	0.458 (4)	0.0897 (7)	0.82	0.80	0.63
6	– –	0.195 (3)	44.9 (2)	0.836 (8)	0.471 (5)	3.21	1.1	9.1
Mean (cv%)	3.2 (57)	0.245 (7)	46.3 (12)	0.515 (35)	0.169 (100)			
Multidose study								
7	11.35 (24)	0.696 (40)	56.0 (3)	2.615 (5)				
8	1.04 (27)	0.0925 (14)	32.8 (13)	0.374 (16)				

Note: Computer estimated parameters are given (with the estimated percentage coefficient of variation in parentheses) together with sum-of-squares of the fit to individual plasma caffeine time curves

$$t_{max} = \frac{2.303}{(k_{ab} - k_{el})} * \log \frac{k_{ab}}{k_{el}} \quad (3)$$

The caffeine-only data (placebo condition) for t_{max} and k_{el} (calculated from $t_{1/2}$) were used to find k_{ab}. The parameters V and k_i were then determined by simulation of the C-t curves via the following procedure. First, the value of V was varied to achieve agreement between the calculated and experimental values for C_{max} and AUC for the caffeine-only data. This provided all the pharmacokinetic parameters for C, which were then used to obtain estimates of k_i from the quinolone treatment data. Second, the value of the inhibition constant k_i was varied in order to obtain agreement between calculated and experimental values of C_{max} and AUC for the C-t curves of C during treatment with the specific quinolone.

Results and discussion

The structures of the five quinolones are shown in Fig. 1.

Development of model

Computer estimated parameters for the plasma C curves in the 6 volunteers in the single dose study and the 2 volunteers in the multidose study are reported in Table 1.

Computer estimates of the percentage coefficients of variation for all parameters are given in parentheses, together with the sum-of-squares (SS) for the fit to each curve. In the single dose study the experimental design did not permit a good estimate of k_{ab}, as the first plasma sample collected usually gave the maximum value. The range was 1.9–3.9 $l \cdot h^{-1}$ for 4 volunteers, with poor estimates for Volunteers 1 and 6. Individual k_{el} values ranged from 0.0615 $l \cdot h^{-1}$ to 0.555 $l \cdot h^{-1}$, (mean 0.246 $l \cdot h^{-1}$). The estimated error (%cv) was 2–3%, except in Volunteer 4, in whom it was larger. The volume of distribution, assuming complete absorption, was 40.6–56.6 l, with a small estimated error. For the effect of PPA in altering caffeine elimination, the inhibition constant k_i was in the range 0.353–0.836 ml·μg^{-1}, and the NFC inhibition constant was much smaller (0.0485–0.471 ml·μg^{-1}, with an estimated error about double the value obtained for PPA). The SS showed a good fit with this model to the data for all volunteers except nos 4 and 6. Results for the multidose study, also given in Table 1, show a good fit to the experimental data. Volunteer 7, the smoker, had larger values for the parameters, as well as a larger SS due to higher plasma values.

In summary, computer analysis of the individual data from the two studies demonstrated that the 1-comparment model for caffeine provided a good description of the C-t curves for both the single and multiple dose studies. The quinolone inhibition effect was also well described by this model with nonlinear elimination.

C-t curves of caffeine for 4 individuals treated with placebo (P), NFC, and PPA are shown in Fig. 2. The placebo curves are linear in the semilog plots, as expected for a 1-compartment model, while the quinolone treatment curves show nonlinear or saturable caffeine elimination. NFC affected the C elimination curves and PPA treatment caused much stronger inhibition of C elimination. Both compounds produced higher plasma levels and a longer elimination time. When the curves for Volunteer 2 were extended further in time, the PPA line finally decayed to parallel the other two. Inspection of the curves for Volunteer 4, where the model gave a poor fit to the data, showed that the PPA curve was almost flat, suggesting that the disposition of C in this subject was strongly inhibited by the doses of PPA and NFC used.

The pharmacokinetic curves for the 2 multidose volunteers are shown in Fig. 3, where the arrows indicate the times at which oral doses of PPA were administered. The model assumes that both V and k_{ab} of C are constant over the 5 days of the study. The effect of PPA treatment was to cause rapid accumulation and a rise in C levels in both subjects.

The saturable nature of the C-t curves, together with the fact that C elimination is primary via metabolic clearance, suggests that the effects of PPA and NFC can be

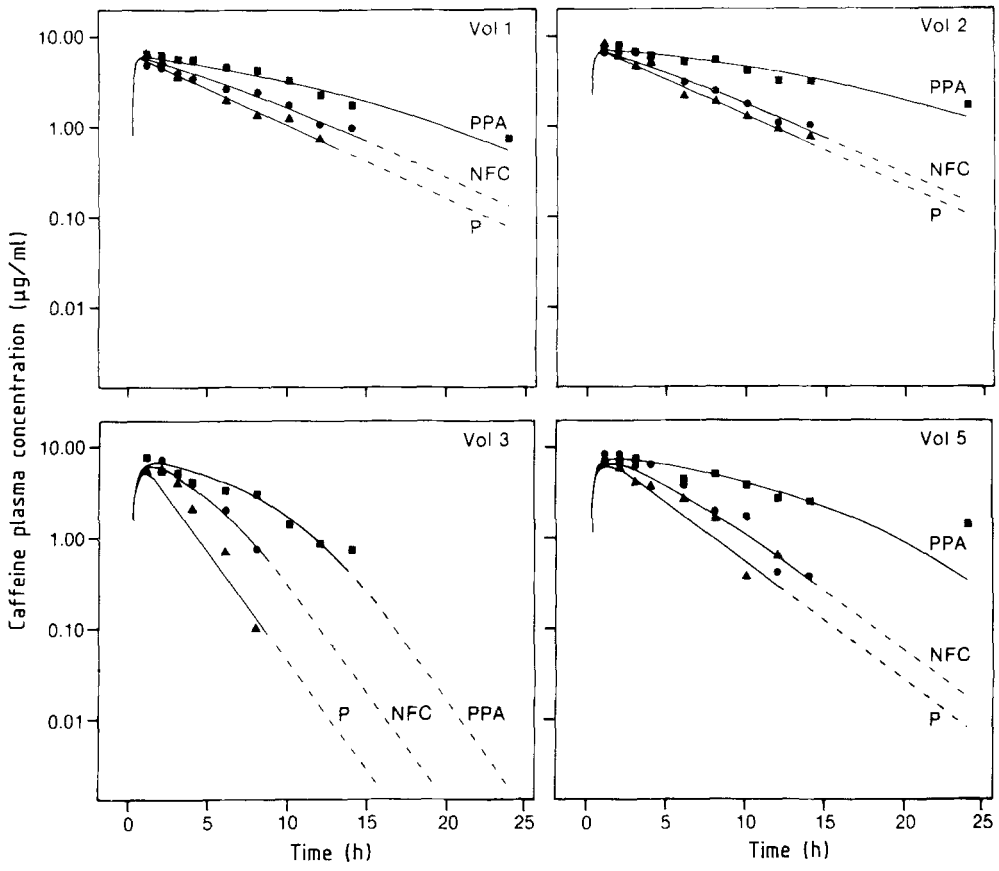


Fig. 2. Semilog concentration-time curves for a single oral dose of caffeine for volunteers treated with placebo (P), pipemidic acid (PPA) or norfloxacin (NFC). The experimental data points are represented by symbols for caffeine with P (▲), PPA (■), and NFC (●). The solid curves are calculated best fits to the experimental data and dotted portions of the curves are extrapolations beyond the experimental data, using the parameters reported in Table 2

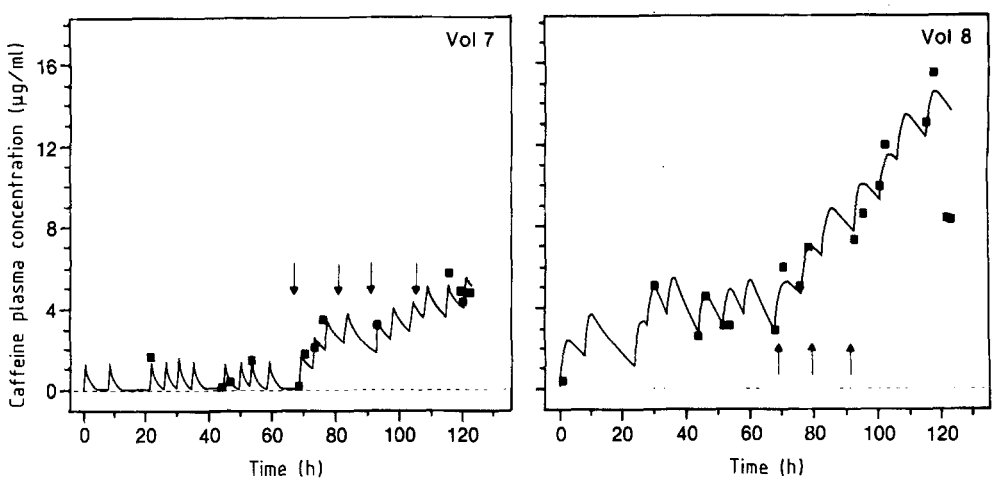


Fig. 3. Linear concentration-time curves for multiple doses of caffeine before and after administration of pipemedic acid (PPA) in two volunteers. The individual data points are represented by symbols for caffeine and the solid curves are calculated best fits to the experimental data, using parameters reported in Table 2

viewed in terms of a Michaelis-Menten mechanism for saturable metabolic clearance. Accordingly, the equation for C with quinolone treatment (Eq. 2 above) can be rewritten in terms of V_{max}, the Michaelis-Menten theoretical maximum rate of elimination, and the Michaelis constant k_M as

$$dC/dt = k_{ab}*f*Dose/V - \frac{V_{max}*C}{(k_M + C)} \text{ treatment} \quad (4)$$

where the constants can be rewritten as

$$k_{el} = V_{max}/k_M \quad (5)$$

and

$$k_i = 1/k_M. \quad (6)$$

The pharmacokinetic parameters for C listed in Table 2 ($t_{1/2ab}$, $t_{1/2el}$, CL_p and V) are typical values for caffeine (Benet and Sheiner 1985). Also listed are the values for the Michaelis-Menten constants (k_M and V_{max} for the NFC and PPA treatments, showing that PPA was a much more effective inhibitor of C than NFC under those experimental conditions.

The rate of C elimination ($\mu g \cdot ml^{-1} \cdot h^{-1}$) versus the C concentration ($\mu g \cdot ml^{-1}$) for placebo, NFC and PPA treatments in the single and multidose experiments do graphed in Fig. 4. As expected, the placebo curves were linear over the entire concentration range of C, while both NFC and PPA showed saturable elimination of C. Clearly, PPA was much more effective than NFC at inhibiting

elimination, as the maximum rate of C elimination was always much lower after the PPA treatment.

Simulations

On the basis of the model developed above for the caffeine-quinolone interaction, computer simulations were carried out on data for CIP, ENX and OFL, where plasma curves for C were altered after treatment with CIP and ENX, and there was little or no change after OFL (Staib et al. 1987). Based on reported values for t_{max} and k_{el}, Eq. 3 was used to estimate k_{ab}. Then V was determined by varying its value in Eq. 1 until agreement was obtained between the experimental and simulated values for C_{max} and AUC. The procedure gave values for V of 45–52 l, in good agreement with the volume of distribution of caffeine reported in Table 1 from direct analysis of individual data. Finally, with all the parameters needed for C in the model, the inhibition constants k_i for the interaction of the 3 quinolones were determined by varying the value of k_i in Eq. 2 until agreement was obtained between the experimental and simulated values of C_{max} and AUC. The values of k_i were CIP 0.2, ENX 1.8 and OFL 0.0 ($ml \cdot \mu g^{-1}$).

The k_i values found for the 3 quinolones are estimates due to the use of average data, and the need to obtain qualitative agreement between calculated and experimental quantities. To demonstrate the relative sensitivity of the simulations in obtaining parameter estimates, results for Volunteer 2 using parameters from Table 1 are presented in Fig. 5. For C with placebo the AUC had a value of approximately 40. With PPA treatment, and a k_i of 0.41, the AUC was increased to 100, whilst a k_i of 0.041 would have given an AUC that was still 15% larger than that of the placebo. The AUC is a more sensitive parameter than C_{max} as a function of k_i, as seen in Fig. 5. An order of magnitude change in k_i resulted in a small change in C_{max}, while the AUC was more than doubled. Thus, it is safe to assume that the range of values found for k_i are reasonable.

Table 2. Pharmacokinetic parameters of caffeine and Michaelis Menten parameters of interactions with norfloxacin and pipemidic acid

Vol	$t_{i/2ab}$ h	$t_{1/2el}$ h	CL_p $l \cdot h^{-1}$	PPA V_{max} $\mu g \cdot ml^{-1}h^{-1}$	PPA k_M $\mu g \cdot ml^{-1}$	NFC V_{max} $\mu g \cdot ml^{-1} \cdot h^{-1}$	NFC k_M $\mu g \cdot ml^{-1}$
Single dose							
1	0.11	3.79	10.4	0.518	2.83	2.00	10.9
2	0.18	3.87	8.52	0.433	2.42	3.69	20.6
3	0.35	1.25	23.7	0.934	1.68	2.12	3.82
4	0.34	11.3	2.80	0.140	2.28	1.26	20.4
5	0.36	2.36	11.9	0.642	2.18	3.28	11.1
6	–	3.55	8.76	0.233	1.20	0.41	2.12
Mean	0.27	4.35	11.0	0.483	2.10	2.13	11.5
(cv%)	(43)	(82)	(63)	(59)	(28)	(58)	(69)
Multidose							
7	0.061	1.00	39.0	0.266	.38		
8	0.67	7.49	3.03	0.247	2.67		

Table 3. Estimated relative potencies of quinolones as inhibitors of caffeine metabolism

Quinolone[a]	Relative potency
enoxacin	100
pipemidic acid	29
ciprofloxacin	11
norfloxacin	9
ofloxacin	0

[a] see text for doses

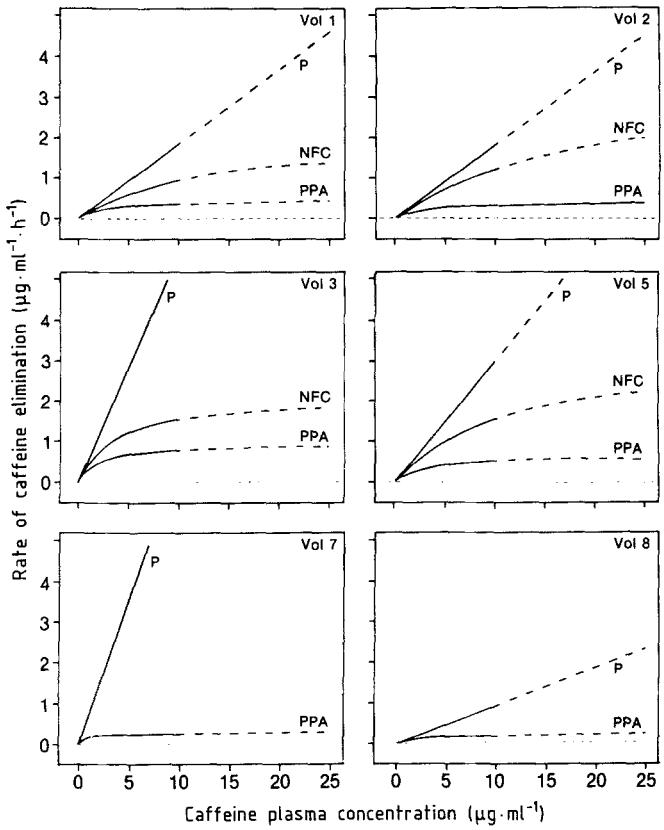


Fig. 4. Rate of elimination versus plasma concentration of caffeine in four volunteers receiving single doses of caffeine (Fig. 1), and two volunteers who received multiple doses of caffeine (Fig. 2). The corresponding Michaelis-Menten constants are reported in Table 2. The solid lines represent the calculated best fit to the experimental data and the dotted portions are extrapolations

Relative potency of quinolones

In Table 3 there is a scale of relative potency of the quinolones as inhibitors of caffeine elimination in humans based on the values obtained for the inhibition constant k_i. ENX was the most potent, OFL had no apparent effect on C elimination, CIP and NFC were equipotent at one-tenth of the strength of ENX, and PPA had a quarter of the potency of ENX. One limitation of the relative potency scale is the clinical protocol used in the studies. The dose of C did not differ much across the 5 studies, but there

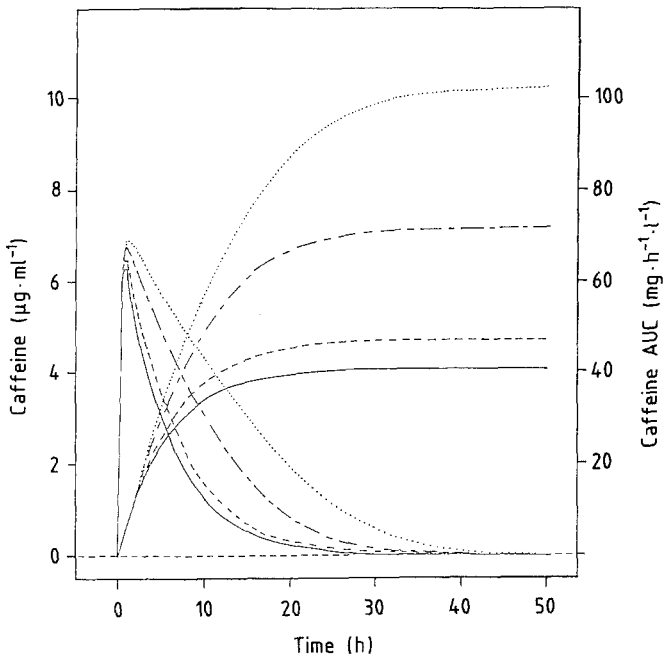


Fig. 5. The effect of inhibition on the plasma caffeine concentration-time curve (left axis) and AUC (right axis) of caffeine in Volunteer 2. No inhibition ($k_i = 0$) is the solid curve, inhibition by pipemidic acid ($k_i = 0.41$) is the highest dotted curve, and smaller inhibition constants are shown as ($k_i = 0.2$) a dot-dash and ($k_i = 0.04$) dashed curves

were considerable differences between the doses of the quinolones used here and recommended therapeutic doses (PDR, 1988). While the ENX dose was equal to the therapeutic recommendation, CIP was studied at one-third of the recommended dose, OFL at half and NFC at twice the recommended therapeutic dose.

Conclusions

A unified model for evaluation of the effect of quinolones on the disposition of caffeine has been developed for the drug-drug interaction that is also directly applicable to other methylxanthines, e.g. theophylline. By application of the model to the clinical data for caffeine a relative potency scale has been obtained for the interaction of caffeine with 5 quinolones. With the value for the strongest inhibitor ENX set at 100, the relative values were ENX 100, PPA 29, CIP 11, NOR 9, OFL 0. The findings have direct application to clinical therapeutic considerations, as it is clear that doses of methylxanthines should be adjusted when they are administered concomitantly with a quinolone.

There are some limitations to the findings due to the experimental design, but they could easily be remedied to provide a more general potency scale for the quinolone-methylxanthine interaction. Future studies with these and other quinolones should use a range of doses of the methylxanthine and the quinolone that would span the recommended therapeutic dose range. Evaluation of steady state conditions is also required. For compounds eliminated from the body primarily by metabolic pathways, it would be extremely valuable to measure plasma levels of the metabolites, to evaluate a range of administered doses and also to measure the plasma levels of the quinolone drugs, in order to ascertain the nature of any inhibition found (Shaw and Houston 1987, Rowland and Martin 1973).

References

Arcieri G, Griffith E, Gruenwaldt G, Heyd A, O'Brien B, Screen P, Becker N, August R (1988) A survey of clinical experience with ciprofloxacin, a new quinolone antimicrobial. J Clin Pharmacol 28: 179–189

Benet LZ, Sheiner LB (1985) Appendix II, Pharmacokinetic constants. In: Gilman AG, Goodman LS, Rall TW, Murad M (eds) Goodman and Gilman's the pharmacological basis of therapeutics, 7th ed. MacMillan, New York, p 1673

Beckman J, Elsaber W, Gundert-Remy U, Hertrampf R (1988) Enoxacin, a potent inhibitor of theophylline metabolism. Eur J Clin Pharmacol 35: 161–165

Berman M, Weiss MF (1975) SAAM Manual, Berman M, Beltz W, Greif P, Chabay R, Boston R (eds) ConSam User's Guide. c/o L. A. Zech, Rm 4B56, Bldg 10, Laboratory of Mathematical Biology, NCI, National Institutes of Health, Bethesda MD 2089

Blanchard J, Sawers SJA (1982) The absolute bioavailability of caffeine in man. Eur J Clin Pharmacol 32: 98–106

Campoli-Richards DB, Monk JP, Price A (1988) Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 35: 373–347

Carbó M, Segura J, de la Torre R, Camí J, Badenas J (1989) Effect of quinolones on caffeine disposition. Clin Pharmacol Therap 45: 234–240

Davies BI, Maesens FPV, Baur C (1987) Ciprofloxacin in the treatment of acute exacerbations of chronic bronchitis. Eur J Clin Microbiol i: 226–231

Edward D, Bowles S, Svensson C, Rybak M (1988) Inhibition of drug metabolism by quinolone antibiotics. Clin Pharmacokin 15: 194–204

Gibaldi M, Perrier D (1982) Pharmacokinetics, 2. ed., Marcel Dekker, New York

Harder S, Staib AH, Beer C, Papenburg A, Stille W, Shah PM (1988) 4-Quinolones inhibit biotransformation of caffeine. Eur J Clin Pharmacol 35: 651–656

Ho G, Tierney M, Dales R (1988) Evaluation of the effect of norfloxacin on the pharmacokinetics theophylline. Clin Pharmacol Ther 44: 35–38

Holmes B, Brogen RN, Richards DM (1985) Norfloxacin: A review of its antibacterial activity, pharmacokinetic properties and its therapeutic use. Drugs 30: 482–513

Khan F, Raoof S (1985) Ciprofloxacin in the treatment of respiratory tract infections. Proceedings of first Symposium of Ciprofloxacin. Leverkussen. Excerpta Medica, Amsterdam, pp 252–256

Nix DE, Schentag JJ (1988) The quinolones: An overview and comparative appraisal of their pharmacokinetics and pharmacodynamics. J Clin Pharmacol 28: 169–178

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

Rall TW (1985) The methylxanthines. In: Gilman AG, Goodman LS, Rall TW, Murad M (eds) Goodman and Gilman's the pharmacological basis of therapeutics, 7th ed. MacMillan, New York, p 589–603

Ramirez-Ronda C, Colon M, Saavedra S, Sabbaj J, Corrado ML (1987) Treatment of urinary tract infections with norfloxacin. Am J Med 82: 75–78

Raoof S, Wollschlager C, Knan F (1985) Serum theophylline levels are increased by ciprofloxacin, a new quinolone antibiotic. Chest 32 (S): 88

Rogge MC, Solomon WR, Sedman AJ, Welling PG, Toothaker RD, Wagner JG (1988) The theophylline enoxacin interaction: I. Effect of enoxacin dose size on theophylline disposition. Clin Pharmacol Ther 44: 579–587

Rowland M, Martin S (1973) Kinetics of drug-drug interactions. J Pharmacokin Biopharm 1: 553–567

San Jose Valverde L, Dominguez AR, Garcia A, Rodriguez M, Blanco JG (1986) Efectos del acido pipemidico sobre el aclaramiento de teofilinas. Rev Esp Allergol Immunol Clin 1: 14–16

Sano M, Yamamoto I, Ueda J, Yokishawa H, Yamashima H, Goto M (1987) Comparative pharmacokinetics of theophylline following two fluoroquinolones coadministration. Eur J Clin Pharmacol 32: 431–432

Sano M, Kawakatsu K, Ohkita C, Yamamoto I, Takeyama M, Yamashina H, Goto M (1988) Effects of enoxacin, ofloxacin and norfloxacin on theophylline disposition in humans. Eur J Clin Pharmacol 35: 161–165

Shaw PN, Houston JB (1987) Kinetics of drug metabolism inhibition; Use of metabolite concentration-time profiles. J Pharmacokinet Biopharm 15: 497–510

Shimizu M, Nakamura S, Takase Y, Kurobe N (1975) Pipemidic acid: absorption, distribution and excretion. Antimicrob Agents Chemother 7: 441–446

Simpson KJ, Brodie MJ (1985) Convulsions related to enoxacin. Lancet II: 161

Staib AH, Harder S, Mieke S, Beer C, Stille W, Shah P (1987) Gyrase-inhibitors impair caffeine elimination in man. Methods Find Exp Clin Pharmacol 9: 193–198

Thomson AH, Thomson GD, Hepburn M, Withing B (1987) A clinically significant interaction between ciprofloxacin and theophylline. Eur J Clin Pharmacol 33: 435–436

Van der Willigen AH, Van der Hoek JCS, Wagenvoort JHT (1987) Comparative double-blind study of 200 and 400 mg enoxacin given orally in the treatment of acute uncomplicate urethral gonorrhea in males. Antimicrob Agents Chemother 7: 535–538

Wijnands WJA, van Herwaarden CLA, Vree TB (1984) Enoxacin raises plasma theophylline concentrations. Lancet II: 108

Wijnands WJA, Vree TB, Van Herwaarden CLA (1986) The influence of quinolone derivatives on theophylline clearance. Br J Clin Pharmacol 22: 677–683

Dr. J. Segura
Department of Pharmacology and Toxicology
Institut Municipal d'Investigació Mèdica
Passeig Marítin 25–29
E-08003 Barcelona, Spain