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Research Papers

Pharmacokinetic interactions of norfloxacin with some metallic medicinal agents

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Summary

The influence of some metallic therapeutic compounds on the pharmacokinetics of orally administered norfloxacin in healthy human volunteers has been examined. The in vitro availability of norfloxacin in dissolution media containing these metallic compounds was also studied. Peak saliva concentration (C_{max}) and bioavailability (AUC_{0-9}) of norfloxacin were reduced by approx. 35-fold, 3–5 fold and 40–50% when co-administered with ferrous sulphate, magnesium trisilicate and potassium citrate, respectively. Concomitant administration with sodium bicarbonate and aluminium hydroxide did not significantly modify the pharmacokinetics of norfloxacin but calcium carbonate reduced its bioavailability by 47%. The absorption and elimination rates of norfloxacin were not affected by the metallic compounds, except potassium citrate which decreased both the absorption and elimination of the drug. There was some degree of correlation between the saliva, urine and in vitro results. Based on the data obtained, it was evident that norfloxacin formed unabsorbable and/or antibacterially inactive/less active complexes with Fe^{2+}, Mg^{2+} and Al^{3+}. Complex formation, adsorption and pH-mediated effects were proposed as factors responsible for the alteration of the pharmacokinetics of norfloxacin by the co-administered agents. There was no clearly discernible link between the valency of the metal ion and its influence on norfloxacin pharmacokinetics.

Introduction

Norfloxacin is a member of the 4-quinolone carboxylic acid derivatives. Although structurally related to nalidixic acid, it demonstrates considerably superior pharmacokinetic and antimicrobial properties with its spectrum of antimicrobial activity covering both gram-negative and gram-positive organisms (Van der Auwera et al., 1985; King and Ian, 1986). Norfloxacin is incompletely absorbed from the gut and about 30% is found unchanged in urine (Eandi et al., 1983). Absorption is claimed to be rapid with peak serum concentrations occurring within 1–2 h in young healthy individuals (Swanson et al., 1983), although MacGowan et al. (1988) have reported a mean time to attain peak concentration of 3.2 h for the aged. However, peak serum concentration is independent of age (MacGowan et al., 1988). The drug penetrates rapidly into body tissues and secretions (Gilfillan et al., 1984; Bergeron et al., 1985).

Although the use of the 4-quinolones is increasing, very little has been published on their interactions with other drugs. There is evidence from

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published works that interaction with other drugs varies with the 4-quinolone type. An antacid product containing Mg^{2+} and Al^{3+} has been reported to inhibit the absorption of the 4-quinolone, ciprofloxacin, resulting in a 6–10-fold decrease in peak serum level but absorption was not hindered by Ca^{2+} (Rubinstein and Segev, 1987). *N*-Butylscopolamine bromide which prolongs gastric emptying retarded the absorption of ciprofloxacin while metoclopramide and piperazine, both facilitators of gastric emptying and intestinal peristalsis, enhanced its absorption (Davey, 1988). Other investigators showed that concurrent administration of xanthines, such as theophylline and caffeine, with ciprofloxacin, enoxacin and perfloxacin produced varying elevated levels of the xanthine, but ofloxacin, another 4-quinolone, did not exhibit a similar interaction (Wijnands and Vree, 1988). 4-Quinolone interactions with the xanthines are pharmacokinetic, with mutual inhibition of metabolic elimination (Davey, 1988).

In the present study, the influence of various co-administered metallic compounds on the pharmacokinetics of norfloxacin in healthy volunteers has been examined. The metallic compounds administered included some of those commonly found in pharmaceutical preparations; one of the objectives was to investigate the link between the valency of the metal ions and the degree of pharmacokinetic interaction.

Materials and Methods

The pure norfloxacin powder used in the preparation of the standard solutions was manufactured by Merck, Sharpe, and Dohme (Paris) and kindly supplied by Associated Pharmaceutical Products Ltd (Lagos, Nigeria). The materials used in the bioassay include nutrient agar (Oxoid, Basingstoke, U.K.) and *E. coli rec.* A Str^R *lac.* as the indicator strain. The metallic compounds administered — magnesium trisilicate, aluminium hydroxide, ferrous sulphate, calcium carbonate, sodium bicarbonate and potassium citrate — were of pharmacopoeial standard and obtained from various sources.

Ten healthy, male volunteers, each of whom gave fully informed consent, took part in this study which had ethical approval. They were between 22 and 25 years old (mean: 23.4 years), 1.67–1.80 m in height (mean: 1.74 m) and weighed between 53 and 72 kg (mean: 61.5 kg). They were non-smokers and had not received any medication in the preceding fortnight. The subjects fasted overnight and each of them took a single dose of 400 mg norfloxacin tablet (Merck, Sharpe & Dohme) with 200 ml of water. After a wash-out period of 2 weeks, the volunteers were divided into two groups of five subjects each. One group then received norfloxacin concurrently with 3 g of tripotassium citrate, 0.5 g of sodium bicarbonate and 0.2 g of ferrous sulphate on successive occasions, allowing a 2-week wash-out interval in each case. The other group similarly ingested norfloxacin with magnesium trisilicate (0.5 g), aluminium hydroxide (0.5 g) and calcium carbonate (0.5 g), also with a 2-week wash-out in between. In all cases, the subjects fasted for at least 4 h after drug administration. For each metallic compound, the administered dose was approximately half the usual adult single dose. Saliva and urine samples were collected from them at the following intervals: 0 (i.e., prior to drug administration), 0.5, 1, 2, 3, 4, 6 and 9 h, and stored at $-16\,^{\circ}C$ until analyzed.

The samples were analyzed using a bioassay procedure based on the British Pharmacopoeia method (1980). Petri dishes were filled to about 4 mm depth with 30 ml of molten nutrient agar which had previously been inoculated with 0.2 ml of an overnight culture of the indicator strain. The plates were allowed to dry for 30 min at room temperature and then four ditches, each 10 mm in diameter, were bored in the medium with a sterile borer. 0.2 ml of the sample of standard solution was placed in a ditch in such a way that the standard solution alternated with the samples. The correlation coefficients of the standard curves usually did not fall below 0.99 and the lower limit of assay sensitivity was 0.005 mg l^{-1}.

In-vitro drug release test

Using a U.S.P. type dissolution apparatus (basket method, Erweka, F.R.G.), the dissolution

of the norfloxacin tablet was examined in 900 ml of 0.1 M HCl (i.e., control) as well as in 0.1 M HCl incorporating 1 g of either magnesium trisilicate, aluminium hydroxide and sodium bicarbonate; 6 g of potassium citrate or 0.4 g of ferrous sulphate (the quantities of these metallic compounds were twice the corresponding doses administered to the volunteers based on our estimation that the volume of gastric fluid in a fasting individual was 450 ml). 5 ml of filtered samples were withdrawn from the dissolution medium over a 45 min period and replaced with an equivalent quantity of the corresponding dissolution fluid. The samples were analyzed as described for the biological samples. 0.1 M HCl was used for the preparation of the standard solutions and the dilution of the samples for assay. All measurements were made in duplicate.

Results

Saliva data

The mean drug concentration vs time curves are plotted in Fig. 1. The computed pharmacokinetic parameters using a two-compartment model are listed in Table 1. The elimination half-life ($T_{1/2\beta}$) was obtained from the logarithmic plot of saliva concentration vs time while the absorption half-life ($T_{1/2\alpha}$) was calculated by the method of 'residuals' (Dittert and Bourne, 1979). The area under the drug concentration vs time curve (AUC_{0-9}) was assessed by the trapezoidal rule (Dittert and Bourne, 1979). The pharmacokinetic parameters for the two groups of subjects were similar when norfloxacin alone was administered. The time taken to reach peak concentration, T_{max} was 2.40–2.60 h, peak concentration (C_{max}) 1.40–

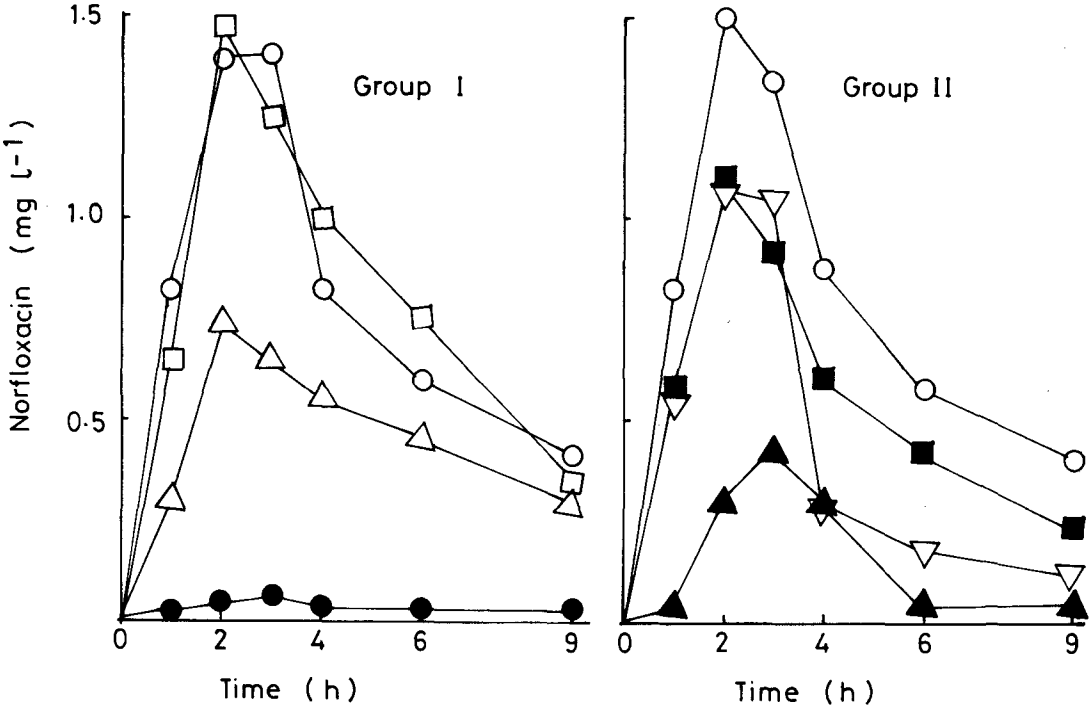

Fig. 1. Mean saliva norfloxacin concentration following oral administration of 400 mg norfloxacin alone (○) and concomitantly with potassium citrate (△), sodium bicarbonate (□), ferrous sulphate (●), aluminium hydroxide (■), magnesium trisilicate (▲) or calcium carbonate (▽).

TABLE 1

Single dose (400 mg) pharmacokinetic data for norfloxacin following concurrent administration with metallic compounds (± S.E.)

	Saliva					Urine	
	T_{max} (h)	C_{max} (mg l^{-1})	AUC_{0-9} (mg h l^{-1})	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	T_{max} (h)	C_{max} (h)
Subject group I							
Norfloxacin alone	2.60 ± 0.25	1.40 ± 0.12	6.95 ± 0.94	0.75 ± 0.09	3.80 ± 0.19	3.00 ± 0.21	531 ± 67
Norfloxacin/K^+	2.40 ± 0.20	0.73 ± 0.08	4.14 ± 0.49	1.08 ± 0.11	5.32 ± 0.49	3.40 ± 0.40	377 ± 80
Norfloxacin/Na^+	2.20 ± 0.20	1.47 ± 0.25	7.29 ± 1.31	0.72 ± 0.14	3.45 ± 0.37	3.00 ± 0.00	565 ± 36
Norfloxacin/Fe^{2+}	2.40 ± 0.25	0.04 ± 0.01	0.23 ± 0.05	0.69 ± 0.17	20.23 ± 5.05	3.20 ± 0.20	161 ± 29
Subject group II							
Norfloxacin alone	2.20 ± 0.20	1.51 ± 0.13	7.01 ± 0.54	0.64 ± 0.07	3.61 ± 0.32	2.80 ± 0.20	631 ± 49
Norfloxacin/Al^{3+}	2.40 ± 0.25	1.09 ± 0.21	4.99 ± 1.35	0.67 ± 0.07	3.47 ± 0.25	2.60 ± 0.25	430 ± 75
Norfloxacin/Mg^{2+}	2.20 ± 0.20	0.43 ± 0.07	1.35 ± 0.21	0.57 ± 0.06	3.31 ± 0.51	3.00 ± 0.20	324 ± 30
Norfloxacin/Ca^{2+}	2.50 ± 0.29	1.08 ± 0.47	3.70 ± 1.61	0.47 ± 0.21	2.13 ± 0.93	2.40 ± 0.25	226 ± 87

1.51 mg l^{-1}; trapezoidal area under the curve (AUC_{0-9}) 6.95–7.01 mg h l^{-1}; $T_{1/2\beta}$ 3.61–3.80 h, and $T_{1/2\alpha}$ 0.64–0.75 h. Concurrent administration with either ferrous sulphate, magnesium trisilicate or potassium citrate significantly reduced (95% confidence level) the C_{max} and AUC_{0-9} of norfloxacin. Sodium bicarbonate and aluminium hydroxide did not exert any significant influence on

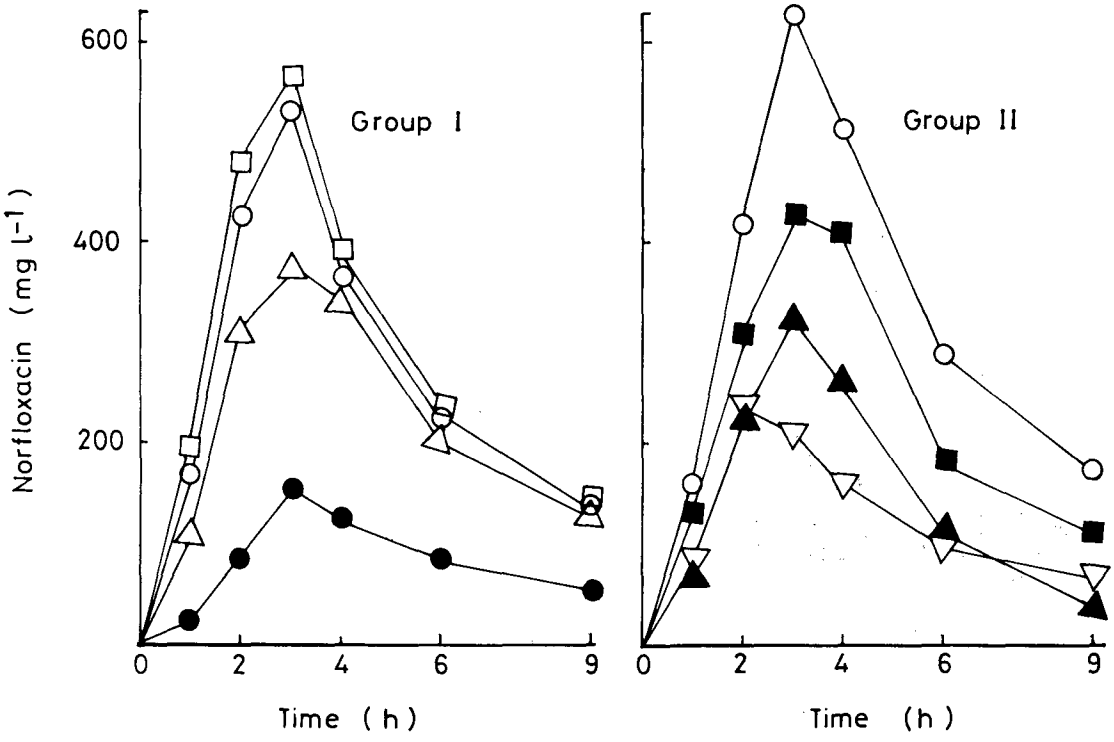

Fig. 2. Mean urine norfloxacin concentration following oral administration of 400 mg norfloxacin alone (○) and concomitantly with potassium citrate (△), sodium bicarbonate (□), ferrous sulphate (●), aluminium hydroxide (■), magnesium trisilicate (▲) or calcium carbonate (▽).

TABLE 2

In vitro percentage availability data for norfloxacin in various dissolution media

Time (min)	Percentage of labelled strength					
	HCl alone (control)	HCl/K^+	HCl/Na^+	HCl/Fe^{2+}	HCl/Al^{3+}	HCl/Mg^{2+}
5	5.9	8.2	4.2	7.8	7.3	8.7
10	13.9	19.4	21.7	17.3	18.3	16.4
45	96.8	96.8	96.8	55.6	73.4	58.8

the pharmacokinetics of the drug, but calcium carbonate lowered only the AUC_{0-9}.

Urine data

The drug concentration vs time plots are illustrated in Fig. 2 and Table 1. T_{max} ranged from 2.40 to 3.40 h and C_{max} from 161 to 632 mg l^{-1}. Only ferrous sulphate, magnesium trisilicate and calcium carbonate significantly altered C_{max}.

In vitro data

The results of the in vitro availability test are outlined in Table 2. The amount of norfloxacin in solution after 45 min was 96.8% of labelled strength of the product for the control (i.e., 0.1 M HCl) as well as the dissolution media containing either sodium bicarbonate or potassium citrate. For the media containing aluminium hydroxide, magnesium trisilicate and ferrous sulphate, the proportions of drug available in vitro were 73.4, and 58.8 and 55.6%, respectively.

Discussion

Norfloxacin penetrates rapidly into saliva. A previous study (Uematsu et al., 1985) indicates that the serum and saliva levels of the drug correlate well, e.g., the T_{max} of the drug in both fluids is 2 h. MacGowan et al. (1988) have also observed that its metabolites are practically absent from serum. None has yet been detected in saliva. The data generated when norfloxacin was administered alone show a high level of similarity with previously published results for both serum and saliva. The T_{max} value of 2.40 h is close to the 2 h reported for saliva and serum by Uematsu et al. (1985) but slightly higher than the 1–2 h obtained for serum by Swanson et al. (1983). The $T_{1/2\beta}$ of the drug in saliva (3.71 h) falls within the range 3.0–5.0 h found in published works (Swanson et al., 1983; Bergan, 1986; MacGowan et al., 1988). The AUC_{0-9} value of 6.98 mg h l^{-1} for saliva compares well with the 6.3 (Swanson et al., 1983) and 7.70 mg h l^{-1} (AUC_{0-8}) (MacGowan et al., 1988) for serum. In addition, the C_{max} of norfloxacin (1.45 mg l^{-1}) from the present study is close to the 1.5–1.6 mg l^{-1} for serum listed by others (Swanson et al., 1983; MacGowan et al., 1988). The indication, therefore, is that saliva is a suitable substitute for serum in the evaluation of norfloxacin pharmacokinetics. Although absorption parameters for drugs are usually determined in serum, we believe that the $T_{1/2\alpha}$ computed in the present study provides a useful basis for estimating the influence of the metallic drugs on norfloxacin absorption, in view of the high degree of similarity of the saliva and serum pharmacokinetics of the drug (which is attributable to its rapid equilibrium distribution into saliva after absorption).

The results (Fig. 1 and Table 1) show that except for sodium bicarbonate and aluminium hydroxide, concomitant administration of the metallic compounds exerted varying degrees of influence on the pharmacokinetics of the 4-quinolone. Both the C_{max} and AUC were lowered in the rank order: $Fe^{2+} > Mg^{2+} > K^+$. Whilst the C_{max} and the bioavailability (AUC) of norfloxacin were reduced approx. 35-fold following concurrent ad-

ministration with ferrous sulphate, the same parameters manifested a 3–5-fold decrease in the presence of magnesium trisilicate. Potassium citrate lowered the magnitude of these parameters by about 40–50%. The fall in the levels of these parameters when the 4-quinolone was given together with aluminium hydroxide was not significant at the 95% confidence level. Although calcium carbonate also did not significantly alter the C_{max} of the drug, it did, however, lower its bioavailability (AUC) by 47%. An earlier study showed that calcium-containing antacids did not affect the pharmacokinetics of another 4-quinolone, ciprofloxacin. The elimination half-life ($T_{1/2\beta}$) and absorption half-life ($T_{1/2\alpha}$) were not modified by the co-administered metallic compounds except potassium citrate which elevated the magnitude of these parameters.

There was a substantial degree of correlation between the in vitro and in vivo availability data. The drug availability in vitro was not affected by sodium bicarbonate and potassium citrate; for the other metallic compounds (except for calcium carbonate for which no result is available) norfloxacin availability was depressed in the following rank order: $Fe^{2+} > Mg^{2+} > Al^{3+}$. A number of factors are believed to be responsible for the changes observed. In a previous paper (Rubinstein and Seger, 1987), it was suggested that the lower serum levels of the 4-quinolone, ciprofloxacin, when it was co-administered with Mg^{2+} and Al^{3+}-containing antacids, were due to the formation of antibacterially inactive chelate complexes between the metallic ions and the drug. Ratcliffe and Smith (1983) had earlier reported a similar phenomenon between Mg^{2+} and some 4-quinolones. The colour change of the dissolution medium containing ferrous sulphate to yellowish brown which was observed during the in vitro dissolution studies on norfloxacin also suggests complexation of Fe^{2+} with the drug. Both the in vitro and in vivo results imply that the norfloxacin-cation complexes formed were unabsorbable and/or antibacterially inactive/less active. The complexation phenomenon was most pronounced in the presence of Fe^{2+}, taking also into account the fact that the dose of ferrous sulphate administered was less than half the dose of either magnesium trisilicate or aluminium hydroxide. It should also be noted that both magnesium trisilicate and aluminium hydroxide are non-systemic antacids; however, the former usually reacts with acid to form Mg^{2+} and silicon dioxide. Silicon dioxide and magnesium trisilicate are known to adsorb a number of drugs (Harvey, 1975). This probably accounts for the greater effect of magnesium trisilicate on both the in vitro and in vivo availability of norfloxacin when compared with aluminium hydroxide.

As the results in Table 1 show, only potassium citrate, of all the metallic compounds, slowed down both the absorption and elimination of norfloxacin. The in vitro data (Table 2) did not provide any evidence of complexation between K^+ and the 4-quinoline. Potassium citrate is a systemic alkalinizer while norfloxacin is a lipid-soluble weak organic acid and therefore shows increased solubility in aqueous solution at alkaline pH (Sabbaj et al., 1986). However, increase in stomach pH facilitates gastric emptying (Gibaldi, 1977) and since norfloxacin is more rapidly absorbed from the stomach, hastened delivery into the small intestine will therefore result in slower absorption. Swanson et al. (1983) have also stated that norfloxacin, with a pK_a of 7.3, is trapped or retained longer in tissue or secretions with higher pH. Thus, systemic alkalinization by potassium citrate may account for the slower elimination of norfloxacin following co-medication with the metallic compound. Although sodium bicarbonate, like potassium citrate, is a systemic alkalinizer, the former apparently did not exert a similar pH-mediated influence on the pharmacokinetics of norfloxacin. A couple of factors are believed to be responsible. First, the dose of sodium bicarbonate administered was only one-sixth that of potassium citrate. Second, it has been reported that the alkalinizing effect of sodium bicarbonate in the stomach is brief and any excess of the compound is rapidly emptied into the intestine (Harvey, 1975). If these factors are considered together with the fact that potassium citrate is a stronger alkalinizer than sodium bicarbonate (pH of a 0.1 M solution being 8.5 and 8.3, respectively), then it can be seen why both compounds did not exert a similar effect on norfloxacin pharmacokinetics.

The in vitro results demonstrate that Na^+, like K^+, did not form an unabsorbable or antibacterially inactive complex with the 4-quinolone.

Urine

Norfloxacin is significantly metabolized, with the metabolites exerting lower antibacterial activity than the parent drug (Borner and Lode, 1986). The bioassay technique employed in the present study does not specifically evaluate the parent drug but provides a measure of the total antibacterial level of the parent drug and its metabolites. Since the metallic compounds co-administered with norfloxacin have not been shown to modify its metabolism, the urine data obtained should constitute a useful basis for examining the influence of the metallic compounds on the pharmacokinetics of the drug in urine. The time taken to attain maximum concentration, T_{max}, ranged from 2.4 to 3.2 h and on average was close to that of saliva. The C_{max} of norfloxacin, to some extent, followed the pattern in saliva, being insignificantly affected ($p < 0.05$) by concomitantly administered sodium bicarbonate, potassium citrate and aluminium hydroxide but lowered by the other metallic compounds in the following rank order: $Fe^{2+} > Ca^{2+} > Mg^{2+}$.

Conclusion

Drug interactions often constitute a major problem in drug therapy. The findings from the present study clearly indicate the need to exercise caution when a patient's condition warrants the administration of norfloxacin and metallic therapeutic agents. Significant pharmacokinetic interactions between norfloxacin and compounds containing Fe^{2+}, Mg^{2+} and K^+ have been established in this study, leading to saliva levels of norfloxacin which fall below the minimum inhibitory concentration (M.I.C.) against streptococcal and staphylococcal species, most strains of *Pseudomonas aeruginosa* and many other pathogens of clinical significance. No definite link appears to exist between pharmacokinetic interactions and the cation valency of the metallic compound. Fe^{2+}, Mg^{2+} and Al^{3+} formed unabsorbable and/or antibacterially inactive/less active complexes with norfloxacin. The monovalent Na^+ and K^+, however, did not complex with the 4-quinolone. The dose of each metallic compound administered in this study was approximately half the usual single adult dose. It is thus likely that the degree of interactions would have been higher if their usual doses were co-administered with norfloxacin. We recommend that there should be a sufficient interval (3 h) between the administration of norfloxacin on the one hand and of compounds containing Fe^{2+}, Mg^{2+}, Al^{3+} and/or K^+ on the other. Further investigation is required in order to determine whether a similar caution should apply to therapeutic agents containing Ca^{2+} and Na^+.

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References

Bergan, T., Quinolones. *Antimicrob. Agents Ann.*, 1 (1986) 164–178.

Bergeron, M.G., Thabet, M., Roy, R., Lessard, C. and Roucault, P., Norfloxacin penetration into human renal and prostatic tissues. *Antimicrob. Agents Chemother.*, 28 (1985) 349–350.

Borner, K. and Lode, H., Biotransformation von Ausgewahlten. *Infection*, 14 (Suppl. 1) (1986) S54–S59.

British Pharmacopoeia. Her Majesty's Stationery Office, London, 1980.

Davey, P.G., Overview of drug interactions with the quinolones. *J. Antimicrob. Chemother.*, 22 (Suppl. C) (1988) 97–107.

Dittert, L.W. and Bourne, D.W.A., Pharmacokinetics. In Banker, G.S. and Rhodes, C.T. (Eds), *Modern Pharmaceutics* Dekker, New York, 1979, pp. 87–142.

Eandi, M., Viano, I., DiNola, F., Leone, L. and Genazzani, E., Pharmacokinetics of norfloxacin in healthy volunteers and patients with renal and hepatic damage. *Eur. J. Clin. Microb.*, 2 (1983) 253–259.

Gibaldi, M., *Biopharmaceutics and Clinical Pharmacokinetics*, Lea and Febiger, Philadelphia, 1977.

Gilfillan, E.C., Pelak, B.A., Bland, J.A., Malatesta, P.F. and Gadebusch, H.H., Pharmacokinetic studies of norfloxacin in laboratory animals. *Chemotherapy*, 30 (1984) 288–296.

Harvey, S.C., Antacids and digestants. In Goodman, L.S. and Gilman, A. (Eds), *The Pharmacological Basis of Therapeutics*, 5th Edn, Macmillan, New York, 1975, pp. 960–975.

King, A. and Ian, P., The comparative in vitro activity of eight newer quinolones and nalidixic acid. *J. Antimicrob. Chemother.*, 18 (Suppl. D) (1986) 1–20.

MacGowan, A.P., Greig, M.A., Clarke, E.A., White, L.O. and Reeves, D.S., The pharmacokinetics of norfloxacin in the aged. *J. Antimicrob. Chemother*, 22 (1988) 721–727.

Ratcliffe, N.T. and Smith, J.T., Effect of magnesium on the activity of 4-quinolone antibacterial agents. *J. Pharm. Pharmacol.*, 35 (Suppl.) (1983) 61P.

Rubinstein, E. and Segev, S., Drug interactions of ciprofloxacin with other non-antibiotic agents. *Am. J. Med.*, 82 (Suppl. 4A) (1987) 119–123.

Sabbaj, J., Hoagland, V.L. and Cook, T., Norfloxacin versus co-trimoxazole in the treatment of recurring urinary tract infections in man. *Scand. J. Infect. Dis.*, 48 (Suppl.) (1986) 48–59.

Swanson, B.N., Boppana, V.K., Vlasses, P.H., Rotmensch, H.H. and Ferguson, R.K., Norfloxacin disposition after sequentially increasing oral doses. *Antimicrob. Agents Chemother.*, 23 (1983) 284–288.

Uematsu, M., Morihana, T., Sekiguchi, T., Imoto, T. and Sasaki, J., The pharmacokinetics and saliva penetration of ofloxacin, norfloxacin, enoxacin and pipemidic acid. *Proc. 14th Int. Congr. Chemother.*, Kyoto, 1985, pp. 1891–1892.

Van der Auwera, P., de Moor, G., Lacroix, G., Mambour, A., Rossion, N. and Schuyteneer, F., In vitro activity of enoxacin compared with norfloxacin and amikacin. *Eur. J. Clin. Microb.*, 4 (1985) 55–58.

Wijnands, W.J.A. and Vree, T.B., Interaction between the fluoroquinolones and the bronchodilator theophylline. *J. Antimicrob. Chemother.*, 22 (Suppl. C) (1988) 109–114.