Br. J. clin. Pharmac. (1992), **33**, 346–348

Milk and yoghurt do not impair the absorption of ofloxacin

PERTTI J. NEUVONEN & KARI T. KIVISTÖ
Department of Pharmacology, University of Turku, Turku, Finland

The effects of milk and yoghurt on the oral absorption of ofloxacin were studied in seven healthy volunteers in a randomized cross-over trial. After an overnight fast, 200 mg ofloxacin was given with 300 ml water, milk or yoghurt. Plasma concentrations and urinary excretion of ofloxacin were determined up to 24 h. Values of total plasma AUC and 24 h urinary excretion of ofloxacin were not affected by milk or yoghurt. Plasma ofloxacin concentrations from 0.5 to 1.5 h and the peak concentration were lower ($P < 0.05$) after yoghurt than without and the time to peak was prolonged by 1 h ($P < 0.05$).

Keywords ofloxacin milk yoghurt absorption interactions

Introduction

Food-drug interactions may occur by many different mechanisms, and they can result in changes both in the rate and extent of absorption (Melander, 1978; Neuvonen & Kivistö, 1989; Welling, 1984). Because of their high calcium content, milk and other dairy products are likely to impair the gastrointestinal absorption of certain drugs, e.g. tetracyclines, which form sparingly soluble chelates with di- and trivalent metal ions (Mattila *et al.*, 1972). Quinolones also bind to the same metal ions forming insoluble chelates (Timmers & Sternglanz, 1978). Accordingly, concomitant ingestion of medications containing iron, aluminium, magnesium, zinc or calcium may interfere with the gastrointestinal absorption of quinolones (Kara *et al.*, 1991; Nix *et al.*, 1989).

A 'standard breakfast' does not appear to impair the absorption of quinolones (Höffken *et al.*, 1988). However, the gastrointestinal absorption of norfloxacin and ciprofloxacin is markedly decreased by the concomitant ingestion of milk or yoghurt (Kivistö *et al.*, 1992; Neuvonen *et al.*, 1991). Because these dairy products contain large amounts of calcium an interaction with ofloxacin seemed likely also. Therefore, a controlled study was designed to investigate this possibility.

Methods

Protocol

A randomized cross-over design with three phases, 1 week apart, was used. Each volunteer was considered to be healthy on the basis of medical history, physical examination and routine laboratory tests (renal and hepatic functions, fasting glucose and haemoglobin). The subjects were informed, both verbally and in writing, and consent was obtained. The study protocol was approved by the ethics committee of the Faculty of Medicine, University of Turku.

Seven male volunteers, with a mean (± s.e. mean) age of 22 ± 2 years and weight of 75 ± 4 kg, participated in the study. After an overnight fast, they were given 200 mg ofloxacin (one 200 mg Tarivid tablet; Hoechst AG, Frankfurt am Main, Germany). Immediately after the ofloxacin tablet, 300 ml water, 300 ml whole milk (containing 360 mg calcium, 9.6 g protein, 11.7 g fat and 14.1 g carbohydrates; Valio, Helsinki, Finland) or 300 ml unflavoured yoghurt (containing 450 mg calcium, 11.4 g protein, 7.5 g fat and 15.0 g carbohydrates; Valio) was ingested. No other food or drinks were ingested during the next 3 h. The subjects could move about as desired.

Timed venous blood samples were collected in heparinized tubes at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 h after drug intake. Plasma was separated within 30 min of sampling. Urine was collected in fractions of 0–10 and 10–24 h. The total volume was recorded and an aliquot was taken for ofloxacin analysis. The samples were stored at −20° C until analyzed.

Analytical methods

Plasma and urine ofloxacin concentrations were measured by h.p.l.c. using a fluorescence detector (Griggs & Wise, 1989). The lower limit of assay was 0.01 μg ml^{-1} in plasma. The interassay coefficient of variation was 3.8% (mean, 0.27 μg ml^{-1} in plasma; $n = 12$).

Correspondence: Dr P. J. Neuvonen, Department of Pharmacology, University of Turku, Kiinamyllynkatu 10, SF-20520 Turku, Finland

Pharmacokinetic analysis

The absorption of ofloxacin was characterized by the peak time (t_{max}), peak plasma drug concentration (C_{max}) and AUC(0,1 h) and AUC(0,24 h), calculated by the linear trapezoidal rule. The area to infinity (AUC) was calculated by adding the AUC(0,24 h) to the area obtained by dividing the 24 h concentration by the terminal elimination rate constant. The elimination half-life ($t_{½,z}$) in plasma was estimated by least squares regression analysis of the terminal concentration-time curve. Urinary recoveries of ofloxacin from 0 to 10, 10 to 24 and 0 to 24 h were calculated.

Statistical methods

The SYSTAT software package (SYSTAT Inc., Evanston, Ill., USA) was used for two-way analysis of variance of the parameters. The parameters were then compared with the control values by Student's *t*-test for paired values (two-tailed), where appropriate. *P* values < 0.05 were considered to be statistically significant. Means ± s.e. means are given. The statistical power to detect a 20% difference in total AUC at $\alpha = 0.05$ was >95% between the control and milk phases, and >97% between the control and yoghurt phases.

Results

Plasma ofloxacin

Neither milk nor yoghurt significantly affected the extent of ofloxacin absorption; total AUC values were 92–94% of the control (Table 1). However, from 0.5 to 1.5 h, the plasma ofloxacin concentration was significantly ($P < 0.05$) lower after yoghurt than without (Figure 1).

Coadministration of yoghurt with ofloxacin prolonged the t_{max} of ofloxacin by 1 h ($P < 0.05$) and reduced the C_{max} by 18% ($P < 0.05$) and the AUC(0,1 h) by 61% ($P < 0.05$). There were no significant differences in the $t_{½,z}$ of ofloxacin between the three phases.

Urine ofloxacin

Neither milk nor yoghurt reduced the cumulative amount of ofloxacin excreted over 24 h. The amount excreted from 10 to 24 h averaged 26–31% of the total amount excreted over 24 h in all groups (Table 1).

Discussion

The results indicate that the absorption of oral ofloxacin is not impaired by concomitant ingestion of a typical volume of milk or yoghurt. The decreased rate of ofloxacin absorption after yoghurt is unlikely to be clinically important.

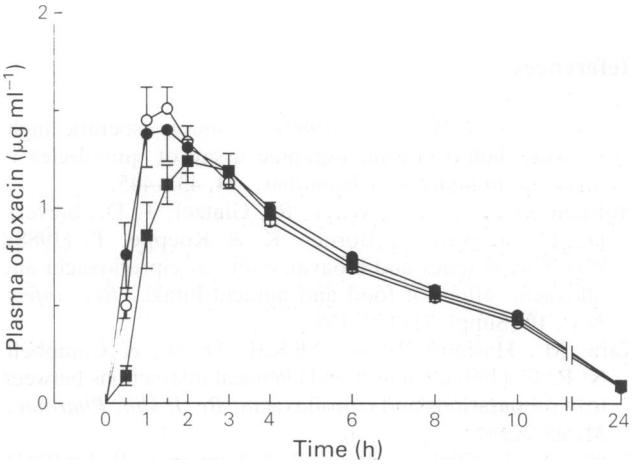

Figure 1 The effect of concomitant ingestion of milk (300 ml) or yoghurt (300 ml) on the plasma concentrations (mean ± s.e. mean) of ofloxacin (200 mg); $n = 7$. + water (•), + milk (○), + yoghurt (■).

Table 1 Effect of milk (300 ml) and yoghurt (300 ml) on the pharmacokinetics of ofloxacin (200 mg)

	Water (control)	*Milk*	*Yoghurt*
Plasma data			
C_{max} (μg ml^{-1})	1.59 ± 0.11	1.62 ± 0.15	1.3 ± 0.09*
t_{max} (h)	1.4 ± 0.28	1.4 ± 0.13	2.4 ± 0.23*
AUC(0,1 h) (μg ml^{-1} h)	0.72 ± 0.12	0.61 ± 0.05	0.28 ± 0.06*
AUC(0,24 h) (μg ml^{-1} h)	12.3 ± 0.67	11.6 ± 0.24	11.2 ± 0.63
AUC (μg ml^{-1} h)	13.0 ± 0.75	12.2 ± 0.25	12.0 ± 0.70
AUC (% of control)	100	94	92
$t_{½,z}$ (h)	5.4 ± 0.11	5.3 ± 0.30	5.7 ± 0.23
Urine data			
Excretion 0–10 h (mg)	112 ± 4.8	117 ± 5.5	110 ± 12.6
Excretion 10–24 h (mg)	41 ± 4.0	41 ± 1.9	49 ± 6.1
Excretion 0–24 h (mg)	153 ± 7.8	158 ± 6.0	159 ± 15.7
24 h excretion (% of control)	100	103	104

Data are mean values ± s.e. mean in seven subjects.
*$P < 0.05$ compared with control.

Ofloxacin seems to differ in its interaction potential from two other quinolones, ciprofloxacin and norfloxacin. The absolute bioavailability of oral ofloxacin is virtually 100% when ingested with water on an empty stomach (Yuk *et al.*, 1991). However, the bioavailabilities of ciprofloxacin and norfloxacin are less complete than that of ofloxacin (Lode *et al.*, 1987) and their absorption is further impaired by concomitant intake of liquid dairy products. Thus, after the ingestion of 500 mg ciprofloxacin, its C_{max} was reduced by 36–47% and its total absorption by 30–36% by the concomitant ingestion of 300 ml milk or yoghurt (Neuvonen *et al.*, 1991). When 300 ml milk or yoghurt was ingested with 200 mg norfloxacin, its C_{max} and total absorption were reduced by about 50% (Kivistö *et al.*, 1992).

The amount of calcium ingested with the quinolones was 360 mg (milk) or 450 mg (yoghurt) both in the present and in the two previous studies. The amounts of other cations in dairy products are negligible. Thus, it appears that either the affinity of ofloxacin for calcium is less than that of ciprofloxacin and norfloxacin or the pharmacokinetic properties of ofloxacin make it less sensitive to this kind of an interaction.

Elderly patients, in particular, may have difficulties in swallowing tablets and capsules. To help swallowing, they often mix the drug with yoghurt or other dairy products. In the case of ciprofloxacin and norfloxacin, this practice may lead to the formation of insoluble calcium-drug complexes and decreased bioavailability. In the case of ofloxacin, however, its absorption seems not to be affected by concomitant use of dairy products.

In conclusion, our findings suggest that ofloxacin can be taken concomitantly with dairy products without compromising its oral absorption.

The authors gratefully acknowledge Mrs Pirjo Ojala-Karlsson, M.Sc, and Ms Paula Nousiainen for the measurement of ofloxacin, and Ms Raija Pitkänen for blood sampling and care of the volunteers.

References

Griggs, D. J. & Wise, R. (1989). A simple isocratic high-pressure liquid chromatographic assay of quinolones in serum. *J. antimicrob. Chemother.*, **24**, 437–445.

Höffken, G., Lode, H., Wiley, R., Glatzel, T. D., Sievers, D., Olschewski, T., Borner, K. & Koeppe, T. (1988). Pharmacokinetics and bioavailability of ciprofloxacin and ofloxacin: effect of food and antacid intake. *Rev. infect. Dis.*, **10** (Suppl. 1), 138–139.

Kara, M., Hasinoff, B. B., McKay, D. W. & Campbell, N. R. C. (1991). Clinical and chemical interactions between iron preparations and ciprofloxacin. *Br. J. clin. Pharmac.*, **31**, 257–261.

Kivistö, K. T., Ojala-Karlsson, P. & Neuvonen, P. J. (1992). Inhibition of norfloxacin absorption by dairy products. *Antimicrob. Agents Chemother.*, (in press).

Lode, H., Höffken, G., Prinzing, C., Glatzel, P., Wiley, R., Olschewski, P., Sievers, B., Reimnitz, D., Borner, K. & Koeppe, P. (1987). Comparative pharmacokinetics of new quinolones. *Drugs*, **34** (Suppl. 1), 21–25.

Mattila, M. J., Neuvonen, P. J., Gothoni, G. & Hackman, R. (1972). Interference of iron preparations and milk with the absorption of tetracyclines. In *Toxicological problems of drug combinations*, eds Baker, S. B. & Neuhaus, G. A., pp. 128–133. Amsterdam: Excerpta Medica.

Melander, A. (1978). Influence of food on the bioavailability of drugs. *Clin. Pharmacokin.*, **3**, 337–351.

Neuvonen, P. J. & Kivistö, K. T. (1989). The clinical significance of food-drug interactions: a review. *Med. J. Aust.*, **150**, 36–40.

Neuvonen, P. J., Kivistö, K. T. & Lehto, P. (1991). Interference of dairy products with the absorption of ciprofloxacin. *Clin. Pharmac. Ther.*, **50**, 498–502.

Nix, D. E., Watson, W. A., Lener, M. E., Frost, R. W., Krol, G., Goldstein, H. & Lettieri, J. (1989). Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. *Clin. Pharmac. Ther.*, **46**, 700–705.

Timmers, K. & Sternglanz, R. (1978). Ionization and divalent cation dissociation constants of nalidixic and oxolonic acids. *Bioinorg. Chem.*, **9**, 145–155.

Welling, P. G. (1984). Interactions affecting drug absorption. *Clin. Pharmacokin.*, **9**, 404–434.

Yuk, J. H., Nightingale, C. H., Quintiliani, R. & Sweeney, K. R. (1991). Bioavailability and pharmacokinetics of ofloxacin in healthy volunteers. *Antimicrob. Agents Chemother.*, **35**, 384–386.

(Received 5 September 1991, accepted 15 November 1991)