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Inhibition of Norfloxacin Absorption by Dairy Products

KARI T. KIVISTÖ,* PIRJO OJALA-KARLSSON, AND PERTTI J. NEUVONEN

Department of Pharmacology, University of Turku, Kiinamyllynkatu 10, SF-20520 Turku, Finland

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Seven healthy subjects received, after an overnight fast, a single 200-mg oral dose of norfloxacin with water, whole milk, and unflavored yoghurt. Coadministration of milk or yoghurt reduced the extent of norfloxacin absorption and the mean peak concentration in plasma by approximately 50%. Taking of norfloxacin with these liquid dairy products should be avoided.

Food-drug interactions have been studied extensively in recent years, but because of the complex nature of these interactions, general guidelines for clinical practice cannot be given (8, 15). Food can influence drug absorption by a wide variety of mechanisms, resulting in changes in both the rate and the extent of bioavailability. The formation of poorly absorbed chelate complexes is one important mechanism of absorption interactions. A classic example is the interference of milk (calcium), iron salts, and antacids containing polyvalent cations with tetracycline absorption (7). Similarly, the absorption of fluoroquinolones is considerably impaired in the presence of cations such as calcium, iron, magnesium, zinc, and aluminum (5, 10–12).

Concurrent ingestion of food with fluoroquinolones has been shown not to interfere with their absorption to a clinically significant degree (4, 6, 14). For example, Frost and coworkers (1) found that the bioavailability of ciprofloxacin is unaffected by a breakfast containing a high amount of calcium. However, we recently demonstrated (9) that the bioavailability of ciprofloxacin is significantly reduced when it is taken together with 300 ml of milk or yoghurt. To our knowledge, the effects of dairy products on the absorption of other fluoroquinolones have not been studied. The objective of this study was to characterize the effects of two liquid dairy products, whole milk and unflavored yoghurt, on the absorption of norfloxacin.

A randomized, three-period, crossover design was used. Each treatment period was separated by a 7-day washout period. Four male and three female volunteers, aged 19 to 24 years and weighing 55 to 90 kg and considered healthy on the basis of medical history, physical examination, and routine laboratory tests, participated in the study. The volunteers were thoroughly informed in writing, and verbal consent was obtained. The study protocol was approved by the ethics committee of the Turku University Medical School.

After an overnight fast, the subjects ingested 200 mg of norfloxacin (one 200-mg Lexinor tablet; Astra Pharmaceuticals, Södertälje, Sweden) with 300 ml of water, 300 ml of whole milk (Valio, Helsinki, Finland), or 300 ml of unflavored yoghurt (Valio). The temperature of water, milk, and yoghurt was 12 to 14°C at the time of administration. The milk and yoghurt portions contained 360 and 450 mg of calcium, 9.6 and 11.4 g of protein, 11.7 and 7.5 g of fat, and 14.1 and 15 g of carbohydrates, respectively. The subjects were allowed to undertake their normal daily activities immediately after receiving the norfloxacin dose; fasting was continued for 3 h. Blood samples for the norfloxacin assay were collected in heparinized tubes before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 h after administration of each drug dose. Plasma was separated within 30 min. Urine was collected at intervals of 0 to 10 and 10 to 24 h; the total volume within each interval was recorded, and an aliquot was taken for norfloxacin analysis. The plasma and urine samples were stored at −20°C until they were analyzed.

Norfloxacin concentrations in plasma and urine were determined by reversed-phase high-performance liquid chromatography as described by Griggs and Wise (3). Plasma standard curves were linear over a concentration range of 0.01 to 2.0 μg/ml. The minimal quantifiable concentration in plasma and the between-day coefficient of variation of the plasma controls were 0.01 μg/ml and 2.9% (mean, 1.08 μg/ml; $n = 13$), respectively.

The peak norfloxacin concentration in plasma (C_{max}) and the time to peak (T_{max}) were obtained by inspection of the individual plasma concentration-time curves. The elimination rate constant (k_{el}) was calculated by weighted, nonlinear least-squares regression analysis by using the reciprocal of the concentrations as the weighting factor. The elimination half-life ($t_{1/2\beta}$) was calculated as $0.693/k_{el}$. The area under the plasma concentration-time curve from 0 to 24 h (AUC_{0-24}) for norfloxacin was calculated by using the linear trapezoidal rule method. The total urinary recovery of norfloxacin following each treatment was used to confirm the effects of dairy products on norfloxacin absorption.

Analysis of variance appropriate for a three-period crossover design was used for analysis of the pharmacokinetic parameters. The parameters of the treatment periods were then compared with the control values, where appropriate, by the Student t test (two-tailed) for paired values. Statistical analyses were performed with the SYSTAT software package (SYSTAT Inc., Evanston, Ill.). P values of <0.05 were considered to be statistically significant. Results are expressed as means ± standard errors.

Norfloxacin concentrations in plasma were markedly decreased by coadministration of milk or yoghurt (Fig. 1). Milk and yoghurt reduced the mean AUC_{0-24} of norfloxacin by 48% ($P < 0.01$) and 58% ($P < 0.01$), respectively (Table 1). A statistically significant decrease was also observed in the mean C_{max}, which was lowered by 51 and 54% when norfloxacin was administered with milk and yoghurt, respectively. The mean T_{max} and $t_{1/2\beta}$ were not significantly affected by the dairy products.

Decreased urinary recovery of norfloxacin also shows that coadministration of dairy products reduced the bioavailability of norfloxacin (Fig. 2). Administration of norfloxacin with milk and yogurt resulted in 40% ($P < 0.05$) and 39% ($P <$

* Corresponding author.

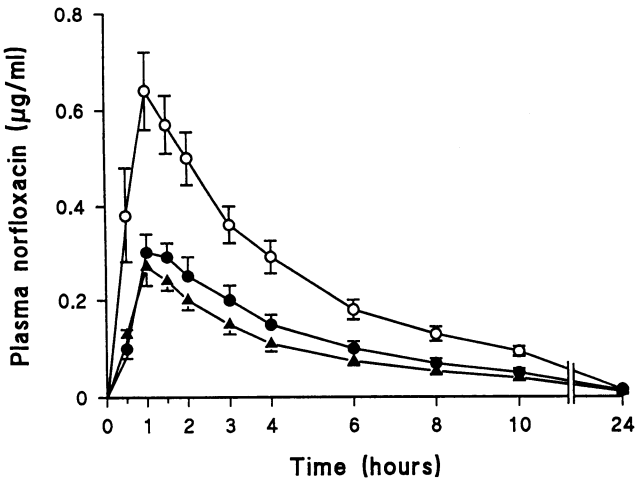

FIG. 1. Norfloxacin concentrations (mean ± standard error) in plasma in seven subjects after intake of a single 200-mg dose of norfloxacin with 300 ml of water (○), 300 ml of whole milk (●), or 300 ml of unflavored yoghurt (▲).

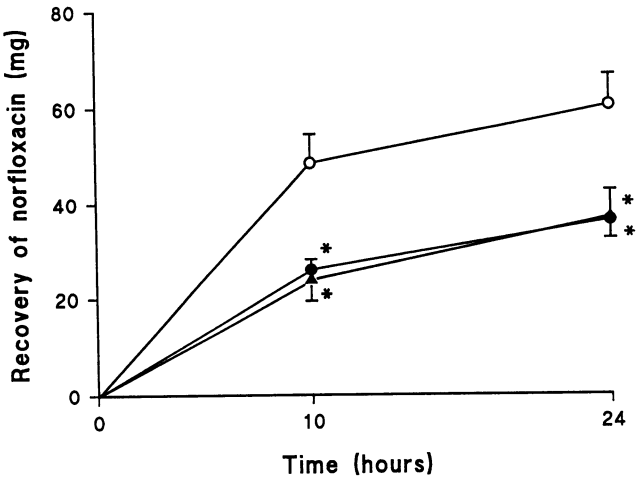

FIG. 2. Cumulative urinary recoveries (mean ± standard error) of norfloxacin in seven subjects after intake of a single 200-mg dose of norfloxacin with 300 ml of water (○; control), 300 ml of whole milk (●), or 300 ml of unflavored yoghurt (▲). *, significantly different from control ($P < 0.05$).

0.05) mean decreases, respectively, in the total amount of norfloxacin recovered in the urine.

We recently demonstrated a significant interaction between ciprofloxacin and dairy products (9); administration of ciprofloxacin with a 300-ml portion of whole milk or unflavored yoghurt resulted in a 30 to 35% decrease in the bioavailability of ciprofloxacin (9). Results of the present study show that liquid dairy products can also interfere with the absorption of norfloxacin; coadministration of milk or yoghurt reduced the absorption of norfloxacin by approximately 50%. The bioavailability relative to that with the control treatment was less than 30% in some subjects, demonstrating the interindividual variability in the extent of this interaction. The dose of norfloxacin (200 mg) was relatively small compared with the 500-mg dose of ciprofloxacin administered in our previous study (9); otherwise, an identical design was used in both studies. The amount of dairy product ingested in relation to the fluoroquinolone dose is probably an important determinant of the extent of the interaction. In the present study, only moderate amounts of dairy products were ingested concomitantly with norfloxacin; higher amounts of milk and yoghurt may result in more severe interference with norfloxacin absorption.

It was recently reported (1) that the extent of ciprofloxacin absorption is unaffected by a breakfast rich in calcium. The breakfast, including 240 ml of whole milk, contained 0.73 g of calcium. In contrast, coadministration of 3.4 g of calcium carbonate (corresponding to 1.36 g of calcium) with ciprofloxacin reduced the bioavailability of the latter by 40% (2). Calcium carbonate had an even greater effect on norfloxacin absorption; administration of 400 mg of norfloxacin 5 min after a 30-ml dose of calcium carbonate mixture (concentration not given) resulted in a relative bioavailability of 38% (11).

Although calcium in solid food does not appear to affect the extent of fluoroquinolone absorption, calcium-containing antacids readily form poorly absorbed chelates with these antibiotics. The concurrent presence of calcium and a fluoroquinolone in the gastrointestinal tract is not the sole prerequisite for the interaction. Calcium ions and quinolone molecules must be dissolved in order to make the chelation reaction possible; this might explain the negligible effect of solid meals on quinolone absorption. Moreover, meal components, e.g., toast slices, may absorb liquid dairy products; in the study of Frost and coworkers (1), the high-calcium meal included a glass of whole milk, yet the absorption of ciprofloxacin was unaffected. Similarly, a fat-rich breakfast, containing, for example, 200 ml of whole milk, did not affect the extent of pefloxacin absorption (13). Antacids containing polyvalent cations have a marked effect on the absorption of fluoroquinolones, which suggests that the gastric pH must be elevated for the chelation to take place. It can be speculated that liquid dairy products can also buffer the acidic gastric contents, especially when they are ingested in a fasting state, and thus facilitate the chelation of quinolones.

Concomitant ingestion of milk or yoghurt would not necessarily hamper the clinical efficacy of oral norfloxacin therapy in the treatment of infections caused by bacteria that normally demonstrate a high level of susceptibility to nor-

TABLE 1. Pharmacokinetic parameters for norfloxacin (200-mg tablet) after each treatment[a]

Treatment	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC_{0-24}		Urine recovery	
				μg · h/ml	% of control	mg	% of control
Water (control)	0.65 ± 0.08	1.07 ± 0.13	5.13 ± 0.35	3.45 ± 0.37	100	60.6 ± 6.3	100
Milk	0.32 ± 0.04[b]	1.36 ± 0.14	8.10 ± 1.9	1.81 ± 0.24[b]	52	36.5 ± 3.9[b]	60
Yoghurt	0.30 ± 0.03[b]	1.14 ± 0.24	7.20 ± 0.79	1.45 ± 0.16[b]	42	37.1 ± 5.8[b]	61

[a] Values are means ± standard errors in seven subjects.
[b] Significantly different from control ($P < 0.05$).

floxacin, e.g., *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Salmonella* and *Shigella* species. These bacteria are inhibited by concentrations of 2 μg/ml or less (4). Furthermore, the high concentrations of the drug achieved in urine following oral administration make a moderate decrease in bioavailability of doubtful clinical significance in the treatment of urinary tract infections. However, some strains of staphylococci and streptococci (*Streptococcus pyogenes* and *Streptococcus pneumoniae*) are more resistant; for streptococci, concentrations of 4 to 16 μg/ml are generally required to achieve 90% inhibition (4). Thus, a potential for decreased activity of norfloxacin against these bacteria may exist if the drug is administered with large amounts of liquid dairy products.

Results of this study demonstrate that both milk and yoghurt can interfere considerably with the gastrointestinal absorption of norfloxacin, and taking of norfloxacin with these dairy products is thus best avoided.

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