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The influence of chronic administration of calcium carbonate on the bioavailability of oral ciprofloxacin

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Six healthy male volunteers participated in a two-period, two-treatment study to determine the effect of chronic calcium carbonate administration on ciprofloxacin bioavailability. There was a mean reduction of 40% in C_{max} and 43% in AUC when calcium carbonate was administered with ciprofloxacin, compared with ciprofloxacin alone ($P < 0.05$). There were no changes in either half-life or t_{max}. It is therefore recommended that patients being treated with ciprofloxacin for serious infections refrain from ingesting calcium supplements. If this is not possible, administration of ciprofloxacin 2 h before ingestion of the supplement is suggested.

Keywords ciprofloxacin calcium carbonate bioavailability interaction

Introduction

Ciprofloxacin is an oral fluoroquinolone with high *in vitro* activity against most gram negative organisms. When administered as a 500 mg tablet, ciprofloxacin is about 70% bioavailable, producing peak serum concentrations of 1.5 to 2.9 μg ml^{-1} (LeBel *et al.*, 1988). Cations such as magnesium, aluminum and iron significantly impair the absorption of fluoroquinolones (Hoffken *et al.*, 1985; Polk *et al.*, 1989) and this has resulted in apparent therapeutic failures (Polk, 1989). Although the mechanism of the interaction is not known, it is thought to involve the formation of non-absorbable chelates (Polk, 1989).

Studies of the interaction between calcium containing antacids and ciprofloxacin have produced conflicting results. Fleming *et al.* (1986) have suggested that calcium carbonate (Titralac capsules) does not affect the absorption of ciprofloxacin, whereas Frost *et al.*, (1992) have shown a 40% decrease in mean bioavailability of ciprofloxacin with concomitant administration of a large single dose of a calcium antacid (Alka-Mint 4 × 850 mg calcium carbonate tablets). Similarly, the effect of calcium-containing foods on ciprofloxacin absorption is controversial. Frost *et al.* (1989) have demonstrated little effect of a high calcium meal on quinolone bioavailability whereas Neuvonen *et al.* (1991) have shown a significant reduction in ciprofloxacin absorption when administered with milk and yogurt.

Calcium carbonate tablets are widely consumed as therapy for patients with osteoporosis and as a calcium supplement. The effect of concomitant calcium carbonate, in this dosage form, on the bioavailability of quinolone antibiotics has not been investigated previously. The purpose of this study was to evaluate the effect of chronically administered calcium carbonate tablets on the absorption of ciprofloxacin.

Methods

Patient selection

The study was approved by the Committee on the Conduct of Human Research, Medical College of Virginia Hospitals, and written informed consent was obtained from the participants. On the morning of each study day, subjects were admitted to the Antibiotic Research Unit of the Biopharmaceutics Centre, School of Pharmacy. Six healthy male volunteers participated in the study. The mean (± s.d.) ages and weights of the subjects were 28.1 ± 4.4 years and 82.2 ± 17.2 kg, respectively. Exclusion criteria were: hypersensitivity to any drug, use of any medications, chronic illnesses, subjects with total body weight deviating greater than 10% from ideal, abnormal physical examination or laboratory values.

Study design and sample collection

Subjects were instructed to avoid all medications throughout the study, and dairy products 72 h before each study day. Subjects refrained from alcohol and

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caffeine consumption beginning 48 h prior to each study day. The participants fasted overnight and for a period of 4 h after each dose of ciprofloxacin.

On the morning of study day 1, subjects received a single dose of ciprofloxacin 500 mg (Miles Pharmaceuticals, New Haven, Conn. Lot CXG8) with 180 ml of tap water. Blood samples were collected before drug administration and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h. On days 2 to 7, subjects received calcium carbonate (Oscal 500 tablets—500 mg elemental calcium, Marion Laboratories, Kansas City, MO, Lot S8371) three times daily with meals. On the morning of study day 8, they received their second dose of ciprofloxacin with a final dose of calcium carbonate. Blood samples were obtained as above. Compliance was assessed by tablet count and subject diary.

Drug assay

The concentration of ciprofloxacin in serum was measured by reverse-phase high performance liquid chromatography with fluorescence detection (Nix *et al.*, 1985). Modifications to the published assay included use of a mobile phase consisting of 13% v/v acetonitrile and 87% v/v phosphate buffer (pH 3.0) and extraction with methylene chloride—isopropyl alcohol (90:10). Peak area ratios of ciprofloxacin to the internal standard (difloxacin [A56619]; Abbott Laboratories, North Chicago, IL) were linear over the concentration range of 0.06 to 10 μg ml^{-1}. Inter-day coefficients of variation ($n = 6$) were less than 10% over the concentration range of 0.25 to 5 μg ml^{-1}.

Data analysis

The terminal elimination rate constant (λ_z) was obtained by least squares regression of the log serum drug concentrations in the log-linear phase. The elimination half-life was calculated by dividing 0.693 by λ_z. The AUC of ciprofloxacin was calculated by the linear trapezoidal rule with extrapolation to infinity using C_t/λ_z, where C_t is the last measured concentration. Peak serum concentration (C_{max}) and the time to peak concentration (t_{max}) were determined directly from the data.

Statistical analysis

Differences in mean pharmacokinetic parameters of ciprofloxacin between treatments were evaluated by a paired *t*-test. All pharmacokinetic data, except λ_z, were logarithmically transformed, and the least-squares geometric and arithmetic means were used in the *t*-test calculations. The Wilcoxon paired-sample test was used to compare median values for t_{max}. Statistical significance was defined as $P < 0.05$. Pharmacokinetic parameters are reported as arithmetic means ± s.d.; t_{max} data are reported as the median values.

Results

The total AUC values for the two regimens were significantly different (Table 1). Concomitant administration of calcium carbonate tablets reduced the mean bioavailability by 43% (range 24 to 58%, $P < 0.05$). Peak concentrations of ciprofloxacin in all subjects were significantly lower compared with concentrations following ciprofloxacin alone (2.9 ± 0.3 *vs* 1.8 ± 0.3 μg ml^{-1}; $P < 0.05$; Figure 1). There were no statistically significant differences in t_{max} (1.0 h alone *vs* 0.75 h with calcium) or half-life (2.80 ± 0.66 alone *vs* 3.17 ± 0.76 h with calcium). No adverse effects were reported with either ciprofloxacin or calcium ingestion.

Table 1 Pharmacokinetic parameters for individual subjects receiving ciprofloxacin alone (A) and with a calcium supplement (B)

Subject	C_{max} ($mg\ l^{-1}$) A	B	*AUC* ($mg\ l^{-1}\ h$) A	B
1	2.7	1.7	15.1	6.4
2	2.7	1.2	11.0	4.6
3	3.2	1.7	11.0	4.6
4	3.4	2.2	13.1	9.8
5	2.5	1.9	9.4	5.5
6	3.1	1.9	11.9	5.5
Mean	2.9	1.8	12.4	7.3
s.d.	0.3	0.3	2.1	2.2
CV%	11.6	18.8	16.7	29.7
Ratio A/B (× 100%)	39.5		42.6	
95% CI	50.1–73.2		43.9–74.9	
P value	0.001		0.003	
Intra-subject CV	12.8%		18.0%	

C_{max}, peak plasma concentration; AUC, area under the plasma concentration-time curve; t_z, time of last measurable concentration; CV, coefficient of variation; CI, confidence interval. Ratio A/B, ratio of least squares geometric mean for C_{max} and AUC.

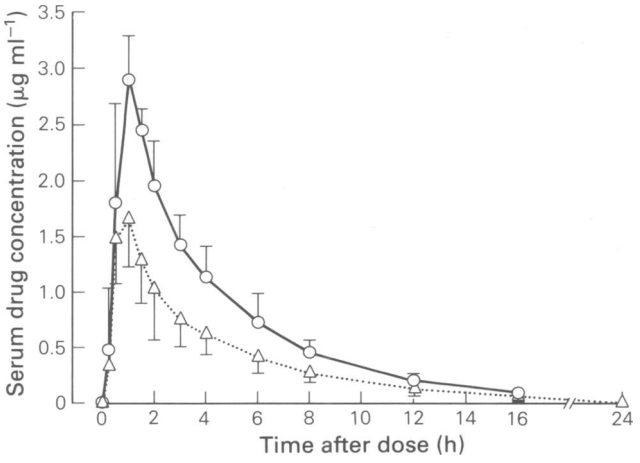

Figure 1 Mean serum concentration (± s.d.) of ciprofloxacin in subjects reciving ciprofloxacin, 500 mg alone (○) and ciprofloxacin plus 500 mg elemental calcium (△).

Discussion

Ciprofloxacin, when administered alone is rapidly absorbed and excreted. The derived pharmacokinetic parameters are in agreement with other published data (Lomaestro *et al.*, 1991; Polk *et al.*, 1989). This study indicates that chronic administration of a calcium supplement, in a recommended dose, significantly impairs the absorption of ciprofloxacin. Frost *et al.* (1992) demonstrated a similar decrease in AUC of ciprofloxacin with concurrent administration of a large single dose of calcium carbonate (1340 mg elemental calcium). In contrast, Fleming *et al.* (1986) did not demonstrate a decrease in C_{max} of ciprofloxacin with concomitant administration of a calcium antacid. However, important details such as the amount of calcium administered are lacking in this report. More recently, a significant interaction (30–36% reduction in ciprofloxacin bioavailability) between high calcium-containing foods and ciprofloxacin has been shown (Neuvonen *et al.*, 1991). These results contradict earlier findings of Frost *et al.* (1989) who demonstrated an increase in quinolone bioavailability when administered with a high fat/high calcium meal.

This discrepancy may be due to the vehicle in which the cation is present. In the former study (Neuvonen *et al.*, 1991), calcium was administered in a liquid form whereas in the latter it was administered in a solid form (cheese). Additionally, Frost *et al.* (1989) used a ciprofloxacin dose of 750 mg whereas Neuvonen *et al.* (1991) used a dose of 500 mg. The resultant pH of the gastric milieu may also be an important determinant of the magnitude of the effect since ionisation of the carboxylic group on the quinolone molecule allows for more effective chelation with the cation (Frost *et al.*, 1992).

The interaction described herein may be clinically important for the treatment of systemic infections caused by relatively resistant organisms. We recommend that patients with serious infections who are receiving oral ciprofloxacin refrain from ingesting calcium supplements. If this is not possible, ciprofloxacin administration 2 h prior to taking the cation is recommended (Lomaestro *et al.*, 1991).

References

Fleming, L. W., Moreland, T. A., Stewart, W. K. & Scott, A. C. (1986). Ciprofloxacin and antacids. *Lancet*, **ii**, 294.

Frost, R. W., Carlson, J. D., Dietz, A. J., Heyd, A. & Lettieri, J. T. (1989). Ciprofloxacin pharmacokinetics after a standard or high-fat/high calcium breakfast. *J. clin. Pharmac.*, **29**, 953–955.

Frost, R. W., Lasseter, K. C., Noe, A., Shamblen, E. C., & Letteri, J. T. (1992). Effect of aluminium hydroxide and calcium carbonate antacids on the bioavailability of ciprofloxacin. *Antimicrob. Agents Chemother.*, **36**, 830–832.

Hoffken, G., Borner, K., Glatzel, P. D., Koeppe, P. & Lode, H. (1985). Reduced enteral absorption of ciprofloxacin in the presence of antacids. *Eur. J. clin. Microbiol.*, **4**, 345.

Lomaestro, B. M. & Bailie, G. R. (1991). Effect of staggered dose of calcium on the bioavailability of ciprofloxacin. *Antimicrob. Agents Chemother.*, **35**, 1004–1007.

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., DeVito, J. M., & Schentag, J. J. (1985). Liquid chromatographic determination of ciprofloxacin in serum and urine. *Clin. Chem.*, **31**, 684–686.

Polk, R. E. (1989). Drug-drug interactions with ciprofloxacin and other fluoroquinolones. *Am. J. Med.*, **87** (suppl. 5A), 76S–81S.

Polk, R. E., Healy, D. P., Sahai, J., Drwal, L. & Racht, E. (1989). Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. *Antimicrob. Agents Chemother.*, **33**, 1841–1844.

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