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Effect of Ferrous Sulfate and Multivitamins with Zinc on Absorption of Ciprofloxacin in Normal Volunteers

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Cations such as magnesium and aluminum significantly impair the absorption of ciprofloxacin. Twelve healthy adult male volunteers participated in this four-way crossover study to investigate the effects of ferrous sulfate and multivitamins with zinc on the absorption of ciprofloxacin. Doses of ciprofloxacin (500 mg) were given 7 days apart and after an overnight fast. Dose 1 was administered alone (regimen A). The subjects then received either a ferrous sulfate tablet (325 mg three times a day; regimen B) or a once-daily multivitamin with zinc (regimen C) for 7 days; dose 2 of ciprofloxacin was then given with the last dose of regimen B or C. Subjects were crossed over to the alternate regimen for 7 days, and dose 3 of ciprofloxacin was again administered with the last dose of regimen B or C. After a 7-day washout, dose 4 of ciprofloxacin was given (regimen D). Ciprofloxacin concentrations were determined by high-pressure liquid chromatography. The areas under the concentration-time curve (AUCs) of ciprofloxacin for regimens A and D were not significantly different (14.5 ± 2.3 versus 15.7 ± 2.8 μg · h/ml, mean ± standard deviation). The AUCs for regimen B (5.4 ± 1.7 μg · h/ml) and regimen C (11.3 ± 2.4 μg · h/ml) were significantly different from the AUCs for regimens A and D. Peak concentrations of ciprofloxacin with regimen B were below the MIC for 90% of strains of many organisms normally considered susceptible. Ferrous sulfate and multivitamins with zinc significantly impaired the absorption of ciprofloxacin. The effect of ferrous sulfate is likely to be clinically significant; the responsible component of multivitamins with zinc requires additional study.

The advantages of the fluoroquinolone antibiotics include excellent in vitro activity for gram-negative aerobic bacilli, a low frequency of adverse effects, and good oral absorption (6, 12). These features may allow the treatment of some infections which previously have required hospitalization and parenteral therapy (1). However, numerous reports have shown that certain cations, such as magnesium and aluminum, can significantly impair the absorption of most fluoroquinolones (4, 5, 7, 9; G. Hoffken et al., Letter, Eur. J. Clin. Microbiol., **4**:345, 1985) and may result in therapeutic failure (M. Noyes and R. Polk, Letter, Ann. Intern. Med., **109**:168, 1988). The purpose of this investigation was to evaluate the effects of another commonly ingested cation, ferrous sulfate (iron), and a multivitamin-with-zinc tablet (MVZ) on the absorption of ciprofloxacin in normal volunteers.

MATERIALS AND METHODS

Volunteers. This study was approved by the Institutional Review Board at the Medical College of Virginia Hospitals. Written informed consent was obtained. The twelve healthy, nonsmoking male volunteers had normal medical histories and physical examinations and routine biochemistries. The mean (± standard deviation) age and weight of the subjects were 28.2 ± 3.7 years and 74.3 ± 6.3 kg. Exclusion criteria included hypersensitivity to any drug, use of medication for chronic illness, and consumption of alcohol within 72 h of each of the four study periods. The subjects were admitted into the Antibiotic Research Unit of the Biopharmaceutics and Pharmacokinetics Center at the School of Pharmacy.

Drug administration and sample collection. The study design was a four-way crossover. The four doses of ciprofloxacin (500 mg each) were given 1 week apart and after an overnight fast. Subjects did not eat for 4 h after dosing. On the morning of study day 1, subjects received ciprofloxacin (Cipro, lot BAC 8; Miles Laboratories, Inc., West Haven, Conn.) with 180 ml of water. Blood samples were collected before drug administration and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after this and all subsequent doses of ciprofloxacin. On the morning of study day 2, after the last blood sample was taken for ciprofloxacin, subjects were assigned to take iron (Feosol, lot no. X1078942; SmithKline Beckman Corp., Philadelphia, Pa.) as a 325-mg tablet three times daily with meals or MVZ (Stresstabs 600 with Zinc, lot no. 214-528; Lederle Laboratories, Pearl River, N.Y.) once daily in the morning. The composition of MVZ is listed in Table 1. The subjects received the assigned regimen during study days 2 through 6. Dose 2 of ciprofloxacin was administered with the final dose of iron or MVZ the morning of day 7. The following morning, the subjects were crossed over to the alternate regimen of iron or MVZ, which was taken through study day 13. The morning of day 14, dose 3 of ciprofloxacin was administered with the final dose of iron or MVZ. After a 7-day washout period, dose 4 of ciprofloxacin was administered.

Subjects voided immediately before each dose of ciprofloxacin and urine was collected for 24 h for ciprofloxacin assay.

Ciprofloxacin assay. The concentrations of ciprofloxacin in serum and urine were measured by high-pressure liquid chromatography, using a modification of the method of Nix et al. (8). Differences included a mobile phase consisting of 13% acetonitrile and 87% phosphate buffer (pH 3.0) and the incorporation of an extraction step with methylene chloride-isopropyl alcohol (90:10). Peak area ratios of ciprofloxacin to an internal standard (difloxacin [A-56619]; Abbott Laboratories, North Chicago, Ill.) were linear over the concentration ranges of 0.1 to 10 μg/ml in serum and 5 to 300 μg/ml in urine. Coefficients of variation were less than 7.8% in serum

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TABLE 1. Composition of MVZ[a]

Component	Amt (mg)
Vitamin E	30
Vitamin B1	15
Vitamin B2	10
Vitamin B3	100
Vitamin B5	20
Vitamin B6	5
Vitamin B12	12
Vitamin C	600
Folic acid	0.4
Zinc	23.9
Biotin	45
Copper	4

[a] Stresstabs 600 with Zinc (Lederle).

and urine. Absolute analytical recoveries of ciprofloxacin were 34.1% at 0.25 μg/ml and 65.2% at 5.0 μg/ml.

Pharmacokinetic analysis. Compartmental and noncompartmental methods were used for analysis of ciprofloxacin data. One- and two-compartment linear models were fit to ciprofloxacin serum concentrations by the least-squares nonlinear regression program PCNONLIN (11). A weighting factor of $1/C^2$ resulted in a significant reduction in the weighted sum of squared residuals. Akaike information criteria were used to compare one-compartment to two-compartment fits (14) and were found to provide similar results. Elimination rate constants (k_{el}) from the weighted one-compartment fits are reported and were used in the calculation of the area under the concentration-time curve (AUC), since the contribution of the extrapolated area from the one-compartment fits was similar to that of the two-compartment fits (4.1 ± 1.9 versus 8.1 ± 4.9%, respectively) and since the one-compartment fits indicated half-lives more consistent with previously reported values (see below). The half-lives were calculated from the equation $t_{1/2} = 0.693/k_{el}$. AUCs for ciprofloxacin during weeks 1 and 4 from 0 to 24 h were calculated by using the linear trapezoidal rule and extrapolated to infinity by adding the term C_{last}/k_{el}, where C_{last} is the last measurable concentration. Ciprofloxacin concentrations during treatments with iron and MVZ could not be analyzed by compartmental methods because the effects of treatment often resulted in concentration-time curves which could not be fit. AUCs for ciprofloxacin during treatments with iron and MVZ were calculated by using the linear trapezoidal rule. If C_{last} was measurable during treatment with iron or MVZ, then the extrapolated area was estimated by linear regression of the concentrations in the log-linear phase, and the term C_{last}/k_{el} was added to the area calculated by the trapezoidal rule. The contribution of the extrapolated area to the total area for treatments with iron and MVZ was <10% for all calculations. Peak concentrations in serum were determined by inspection.

Differences in AUCs, peak concentrations in serum, and 24-h urine recovery with the four regimens were assessed by two-way analysis of variance. The Scheffe multiple range test was used to identify differences between treatment periods. A probability value of <0.05 was considered statistically significant.

RESULTS

The bioavailability of ciprofloxacin has been reported to show a poor correlation to dosage when repeated doses are administered to the same individual (10). We designed this study to evaluate the within-subject reproducibility of absorption and the effects of iron and MVZ by administering the final dose (week 4) and the first dose (week 1) under identical conditions.

TABLE 2. AUCs for ciprofloxacin administered on empty stomach (week 1 and week 4), with ferrous sulfate (iron), and with MVZ

Subject	Ciprofloxacin AUC (μg · h/ml)[a]			
	Nothing (wk 1)	Iron	MVZ	Nothing (wk 4)
1	12.80	4.19	9.64	12.60
2	16.61	4.05	8.48	17.29
3	14.80	4.33	10.96	19.19
4	13.19	6.35	10.94	17.63
5	12.00	2.84	7.78	17.81
6	14.21	5.15	8.75	12.11
7	13.24	5.25	13.17	13.64
8	19.67	8.18	15.32	19.67
9	13.38	3.38	11.04	12.91
10	14.24	8.04	11.94	12.05
11	12.05	6.20	12.15	16.70
12	17.40	6.49	15.03	16.96
Mean ± SD	14.46 ± 2.33	5.37 ± 1.72	11.29 ± 2.42	15.71 ± 2.84

[a] There is no significant difference between the values for weeks 1 and 4. AUCs of ciprofloxacin with iron and MVZ are significantly different from each other and from AUCs for weeks 1 and 4.

There was no significant difference in half-lives for weeks 1 and 4 (3.9 ± 1.1 versus 4.2 ± 1.2 h, respectively; $P > 0.05$). By analysis of variance, there was a statistically significant difference in peak concentrations in serum with the four treatments ($F = 54.8$, $P < 0.0001$). There was no significant difference between weeks 1 and 4 (2.8 ± 0.8 versus 3.2 ± 0.8 μg/ml, respectively). Mean peak concentrations of ciprofloxacin in subjects taking iron (0.7 ± 0.4 μg/ml) and MVZ (1.9 ± 0.5 μg/ml) were significantly lower than the peak concentrations in weeks 1 and 4 and were significantly different from each other ($P < 0.01$).

By analysis of variance, there was a statistically significant difference in AUCs for the four regimens ($F = 75.6$, $P < 0.0001$). There was no significant difference in AUCs for weeks 1 and 4 (14.66 ± 2.33 versus 15.71 ± 2.84 μg · h/ml, respectively; Table 2). The AUCs for the regimens containing iron and MVZ were significantly different from each other and from those for weeks 1 and 4 (5.37 ± 1.72 versus 11.29 ± 2.42 μg · h/ml, respectively; $P < 0.01$). The percent reduction in bioavailability for each subject was calculated by comparing the AUC for ciprofloxacin following iron or MVZ to the average of the AUCs from weeks 1 to 4 for the same subject. Concomitant administration of iron reduced the mean bioavailability of ciprofloxacin by 64% (range, 39 to 81%). MVZ resulted in a mean reduction of 24% (range, 2 to 50%) in bioavailability. Mean concentration-time curves are shown in Fig. 1.

The effect of treatment on urinary excretion of ciprofloxacin was similar to the effect on serum. There was no significant difference between weeks 1 and 4 in the cumulative amount excreted over 24 h (130 ± 36 versus 148 ± 46 mg, respectively). Excretion was significantly less with iron and MVZ (30 ± 16 and 86 ± 37 mg, respectively; $P < 0.01$), and these levels were significantly different from each other ($P < 0.01$).

DISCUSSION

Since the initial report on the detrimental effects of magnesium- and aluminum-containing antacids on the absorption

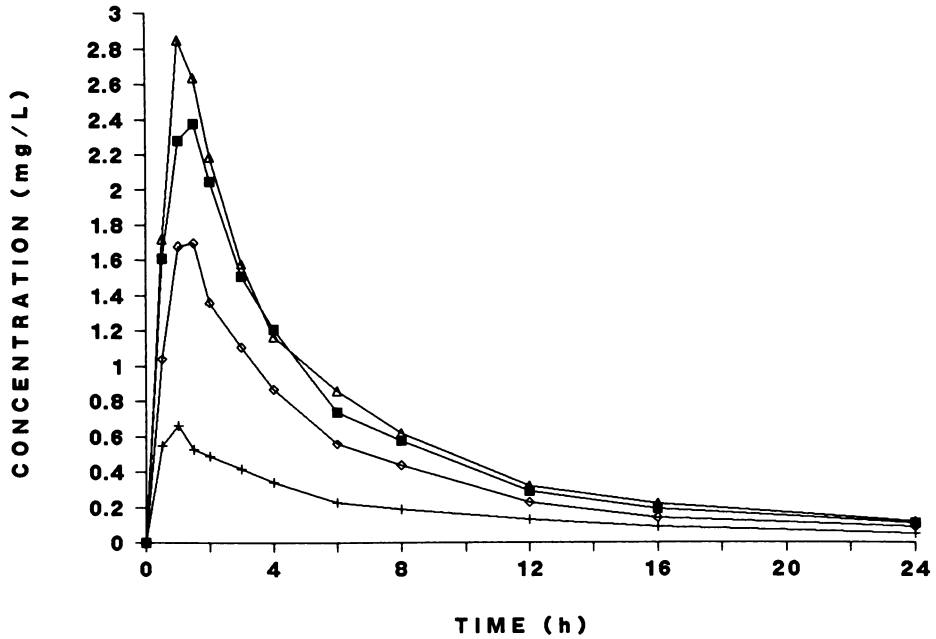

FIG. 1. Mean ciprofloxacin concentrations in serum following fasting (week 1 [■] and week 4 [△]), with iron (+), and with MVZ (◇).

of ciprofloxacin (G. Hoffken et al., Letter), numerous investigations have confirmed and extended these data. All fluoroquinolones studied to date are adversely affected by magnesium-aluminum antacids and aluminum hydroxide (4, 5, 7, 9). Calcium also decreases the absorption of ciprofloxacin (R. Frost et al., Clin. Pharmacol. Ther., **45**:165, 1989). The present investigation is the first to evaluate the effects of ferrous sulfate and MVZ on the bioavailability of ciprofloxacin. Concentrations of ciprofloxacin in serum during weeks 1 and 4 were similar to those previously reported (6). A statistically significant reduction in absorption of ciprofloxacin occurred when iron or MVZ was coadministered.

Quinolones chelate divalent and trivalent cations in vitro (3, 12), and formation of nonabsorbable chelates is the most commonly proposed mechanism to explain the in vivo interaction. Chelation probably occurs between the cation and the 4-keto oxygen and 3-carboxylic acid groups of the quinolone (12). Clinical investigations have usually evaluated the effect of cation-containing antacids on fluoroquinolone absorption (4, 5, 7, 9). Thus it is possible that changes in local pH or the absorbing properties of the gel, in addition to chelation, cause reduced absorption of the quinolone. Our investigation indicates that chelation alone may have a significant effect, since neither iron nor multivitamins with zinc should affect local pH. It is also possible that ferrous salts have a nonspecific effect on the absorptive capacity of the gastrointestinal tract, as iron has recently been reported to impair the absorption of methyldopa, a drug which appears not to chelate iron (2).

The data from this study strongly suggest that patients receiving ferrous sulfate three times a day should not receive oral ciprofloxacin concomitantly, since peak concentrations in serum are below the MIC for 90% of strains of some organisms normally considered susceptible (13). It is not known whether this interaction can be avoided by staggering administration times or whether smaller doses of iron, such as those found in many multivitamin preparations, have a similar effect.

While the effect of MVZ on the absorption of ciprofloxacin is statistically significant, the magnitude of the effect is significantly less than the effect of ferrous sulfate, and the clinical significance is less clear. In the treatment of urinary tract infections, efficacy is not likely to be adversely affected, since concentrations in urine would greatly exceed inhibitory concentrations for most urinary pathogens. However, in the treatment of systemic infections caused by moderately susceptible pathogens such as *Pseudomonas aeruginosa*, it may be advisable to discontinue MVZ during treatment or stagger the administration times. Although zinc is probably responsible for the interaction, we cannot exclude the possibility that other components of the tablet contribute. At least in part, the difference in cation dose in this study (23.9 mg of zinc per day versus 195 mg of iron per day) is likely responsible for the greater effect of iron on bioavailability of ciprofloxacin. Therefore, we recommend that patients receiving ciprofloxacin not receive supplemental zinc until this issue is more fully examined.

Until future investigations identify strategies to avoid the effect of ferrous sulfate on the absorption of ciprofloxacin, we recommend that pharmaceutical products containing iron be avoided by the patient taking ciprofloxacin and possibly all fluoroquinolones. Products containing multivitamins with zinc should also be avoided by patients receiving ciprofloxacin for systemic infections caused by relatively resistant organisms.

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