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Effect of Staggered Dose of Calcium on the Bioavailability of Ciprofloxacin

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The effect on ciprofloxacin's bioavailability (F) of calcium carbonate given 2 h before ciprofloxacin administration in 12 male volunteers was studied. The relative F with calcium was 0.98, maximum concentration of drug in serum increased significantly from 1.98 to 2.42 mg/liter ($P = 0.039$), and time to maximum concentration of drug in serum decreased from 1.82 to 1.26 h ($P = 0.038$). Thus, a single calcium carbonate dose, administered 2 h before ciprofloxacin, does not alter the F of this quinolone.

Ciprofloxacin is an orally administered broad-spectrum antibiotic with activity against multiply drug-resistant organisms (19). All quinolones are subject to several drug-drug interactions affecting absorption, such as the formation of inactive quinolone-chelate complexes with various cations (17). Magnesium- or aluminum-containing antacids may almost completely inhibit ciprofloxacin absorption (6), and patients taking these antacids should use an alternative antibiotic class (11) or have a 2-h interval between doses of cation-containing antacids and quinolones (2). Calcium (18), iron (16), and zinc (16) have also been found to decrease the bioavailability (F) of coadministered ciprofloxacin. Sucralfate may also reduce the absorption of quinolones (12, 14), probably by releasing aluminum in the gastrointestinal tract.

A recent study documented the frequencies of coadministration patterns of ciprofloxacin and cations (10). The significance of the interaction between calcium and ciprofloxacin is controversial, and reports are conflicting (4, 5, 13). The effects of spaced-interval dosing of calcium supplements and ciprofloxacin have not been evaluated. We therefore studied the effects of a 2-h interval between doses of calcium carbonate and ciprofloxacin on the F of ciprofloxacin.

This study was approved by the Institutional Review Board. Written, informed consent was obtained from all participants. Inclusion criteria were as follows: subjects were male, between 18 and 70 years of age, and in good health as determined by medical history. Exclusion criteria were current therapy with any medication within 2 weeks prior to the study, a history of drug allergy, alcoholism or drug abuse, psychiatric or seizure disorders, and thyroid or pulmonary disease. The mean age ± standard deviation of our 12 volunteers recruited was 33.4 ± 6.3 years (range, 21 to 43 years), and their mean weight ± standard deviation was 77.8 ± 7 kg (range, 60 to 118 kg). One volunteer weighed more than 20% over his ideal body weight.

The study design was a nonblinded crossover, in which each individual served as his own control, and consisted of two phases. On the morning of each phase, an indwelling peripheral venous catheter was placed for blood sampling and was kept patent with 2 ml of heparin flush (10 U/ml). On the morning of phase 1, each individual received a single 500-mg dose of ciprofloxacin (Cipro; Miles Laboratories, Inc., West Haven, Conn.) with approximately 100 ml of water. Blood samples (5 ml) were drawn prior to administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after administration of the dose. Seven days later, a single 500-mg dose of elemental calcium (as calcium carbonate, 1,250-mg tablets; Roxane Laboratories, Inc., Columbus, Ohio) was administered 2 h prior to a single 500-mg dose of ciprofloxacin. Volunteers were required to fast from 12 h prior to until 2 h after ciprofloxacin ingestion. Water ingestion was not restricted. Blood samples were collected as described above. Blood (5 ml) was withdrawn from the catheter and discarded before each 5-ml sample was drawn. The blood sample was allowed to clot, and the serum was separated by centrifugation within 1 h of collection. The serum was frozen at −20°C until assayed. All ciprofloxacin and calcium doses were obtained from the same lot of each agent.

Ciprofloxacin concentrations in serum were assayed by using a previously described high-pressure liquid chromatography (HPLC) method (8). Two separate but overlapping serum standard curves were prepared (5.0 to 0.125 and 1.0 to 0.02 mg/liter). Coefficients of correlation were >0.999. Within-run reproducibility was assessed by using spiked serum ($n = 10$) at 3 and at 0.25 mg/liter. Correlation coefficients were 2.3 and 3.1%, respectively. Between-run reproducibility was assessed with a pooled-serum sample with an assay value of 0.49 mg/liter for both the high and the low range. Coefficients of variation between days were 3.4% (high range, $n = 13$) and 3.7% (low range, $n = 14$).

Areas under the ciprofloxacin serum concentration-time curve (AUCs) were calculated both from a noncompartmental model, by using a trapezoidal method, and from data fitted to a two-compartment linear model, by using the RSTRIP program (MicroMath Scientific Software, Salt Lake City, Utah). The AUCs from time zero to the last measured concentration (AUC_{0-12}) and the extrapolated AUC from time zero to infinity ($AUC_{0-\infty}$) were calculated from both methods. $AUC_{0-\infty}$ was calculated by using the last measured concentration in serum for the compartmental model. For the noncompartmental model, the assumption was made that the last three measured concentrations were linear, and the elimination rate constant (k_{el}) was calculated from these

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TABLE 1. Ciprofloxacin pharmacokinetic parameters for individual subjects determined by using a compartmental model

Subject and phase[a]	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-12}[b] (mg · h/liter)	$AUC_{0-\infty}$ (mg · h/liter)	$t_{1/2\beta}$ (h)	k_{el} (h^{-1})	F ($AUC_{PHASE\ 2}$/ $AUC_{PHASE\ 1}$)
1							
1	1.08	3.41	8.50	9.99	2.38	0.291	1.03
2	1.53	1.73	9.29	10.29	3.20	0.216	
2							
1	1.02	3.14	7.74	8.68	2.27	0.305	1.01
2	1.39	1.88	8.20	8.75	2.68	0.259	
3							
1	1.71	1.35	10.15	11.31	3.52	0.197	0.86
2	1.92	1.02	9.23	9.71	2.69	0.257	
4							
1	1.37	2.96	11.24	14.57	4.82	0.144	1.02
2	1.80	1.68	12.36	14.87	4.40	0.157	
5							
1	1.03	1.79	6.34	6.94	3.13	0.221	1.55
2	1.32	2.47	9.44	10.74	3.39	0.205	
6							
1	1.31	1.38	7.47	8.19	3.21	0.216	0.90
2	0.83	3.28	6.46	7.41	2.29	0.303	
7							
1	1.41	2.69	10.05	11.24	2.92	0.237	1.06
2	1.61	2.48	10.69	11.54	2.49	0.279	
9							
1	0.92	3.84	7.93	9.64	2.69	0.258	1.25
2	1.30	3.13	9.95	11.06	2.37	0.292	
10							
1	1.39	2.87	10.39	11.69	3.00	0.231	0.58
2	1.02	1.86	6.06	6.49	2.76	0.251	
12							
1	1.22	2.17	8.59	10.14	3.93	0.176	1.02
2	1.71	1.46	8.78	9.41	2.57	0.270	

[a] Phase 1 is without calcium, and phase 2 is with calcium.
[b] AUC_{0-12} represents the area up to the last measured concentration in serum.

data. The $AUC_{0-\infty}$ was calculated by using this value of k_{el} and the last measured concentration. In addition, the time to peak concentration of drug in serum (T_{max}), peak concentration in serum (C_{max}), half-life of elimination ($t_{1/2\beta}$), and k_{el} were determined from both methods and for both phase 1 (without calcium) and phase 2 (with calcium). For the noncompartmental model, C_{max} and T_{max} were both determined as the time to the highest measured concentrations. For compartmental data, these values were obtained from visual inspection of the fitted curve. The means and standard deviations of each of these pharmacokinetic parameters were determined, and the differences between them for phases 1 and 2 were determined by using a two-tailed Student's t test. A probability of less than 5% was taken as statistically significant. The relative F of ciprofloxacin under the potential influence of calcium was calculated as $AUC_{PHASE\ 2}/AUC_{PHASE\ 1}$. F was calculated for each individual by using AUCs from both compartmental and noncompartmental models, and the mean values of F were reported.

Calculated ciprofloxacin pharmacokinetic parameters for each subject are shown in Tables 1 and 2 for compartmental and noncompartmental models, respectively. Table 3 shows the mean values of the parameters and the percent difference and P values between phases 1 and 2. Administration of calcium carbonate 2 h before ciprofloxacin administration did not alter F. Mean F was 0.98 and 1.03 from noncompartmental and compartmental models, respectively, but there was a large interpatient variability. There was a 0.25 to 3% difference in the AUCs of phases 1 and 2. For noncompartmental data, calcium administration significantly increased C_{max} and decreased T_{max}. There was a significant increase in C_{max} for fitted data. There was a nonsignificant trend to a decrease in $t_{1/2\beta}$ during phase 2 for compartmental and noncompartmental models. In comparing compartmental with noncompartmental models, there was no change in AUCs, $t_{1/2\beta}$, or k_{el}, but large differences were observed in T_{max} and C_{max} (Table 3). Ciprofloxacin and calcium carbonate ingestion was well tolerated by all participants.

Successful ciprofloxacin therapy depends on attainment of adequate concentrations of drug in serum or urine following oral administration. In normal volunteers, the F of ciproflox-

TABLE 2. Ciprofloxacin pharmacokinetic parameters for individual subjects determined by using a noncompartmental model

Subject and phase[a]	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-12}[b] (mg · h/liter)	$AUC_{0-\infty}$ (mg · h/liter)	$t_{1/2\beta}$ (h)	k_{el} (h^{-1})	F ($AUC_{PHASE\ 2}$/ $AUC_{PHASE\ 1}$)
1							
1	2.51	2.00	10.544	12.098	3.365	0.206	0.93
2	2.49	1.00	9.991	11.229	3.576	0.194	
2							
1	2.12	1.983	9.978	11.115	3.280	0.211	0.90
2	2.8	0.97	9.262	10.003	3.210	0.216	
3							
1	2.2	1.483	10.078	11.653	4.200	0.165	0.89
2	2.94	1.016	9.679	10.418	3.420	0.203	
4							
1	1.67	1.566	11.642	15.15	4.960	0.140	1.07
2	2.42	0.933	12.658	16.266	5.680	0.122	
5							
1	1.1	1.583	6.351	7.097	3.450	0.201	1.78
2	2.53	2.00	10.512	12.634	4.900	0.141	
6							
1	1.3	1.32	7.519	8.291	3.345	0.207	0.73
2	2.54	1.55	10.685	11.308	2.401	0.289	
7							
1	1.84	1.50	10.665	12.118	3.470	0.200	1.10
2	2.26	1.583	11.569	13.295	3.987	0.174	
8							
1	2.36	1.31	11.296	13.165	4.047	0.171	1.10
2	3.19	1.00	12.514	14.513	4.616	0.150	
9							
1	2.04	2.816	10.317	12.073	4.056	0.171	1.09
2	1.96	1.583	11.063	13.103	4.418	0.157	
10							
1	2.38	1.15	11.442	13.375	4.060	0.171	0.52
2	1.37	1.50	6.308	6.901	3.157	0.220	
11							
1	2.17	3.016	9.271	11.805	5.489	0.126	0.77
2	2.23	0.533	8.141	9.134	3.822	0.181	
12							
1	2.04	2.166	9.149	11.024	4.481	0.155	0.89
2	2.34	1.48	9.241	9.817	2.347	0.295	

[a] Phase 1 is without calcium, and phase 2 is with calcium.
[b] AUC_{0-12} represents the area up to the last measured concentration in serum.

acin averages approximately 70%, but a highly variable F is noted when repeated doses are administered to the same individual (15). Our results also demonstrated a highly variable intersubject F, with similar numbers of subjects having higher and lower values of F, and are similar to those reported by Crump et al. (3). Two subjects, numbers 5 and 10, had high and low values of F, respectively. These individuals were the same age and of similar weight. It is possible that these differences could be accounted for by differences in gastrointestinal transit time.

Calcium is absorbed in the duodenum and the proximal segment of the small intestine; a smaller percentage is absorbed in the more distal segments of the small intestine (1). Absorption may be influenced by hypocalcemia, pregnancy and lactation, and conditions which increase the rate and extent of absorption (1). The F of calcium, in the form of calcium carbonate, has been reported to be between 9 and 37% (7). A highly variable F has been noted with commercially available calcium carbonate products (9). Thus, a large proportion of calcium remains in the gastrointestinal tract and may have a prolonged availability for potential interaction with quinolones.

Under ideal circumstances of drug absorption and with healthy volunteers, we did not observe a change in ciprofloxacin F resulting from staggered doses of calcium carbonate. It is not possible to accurately infer the effects of this

TABLE 3. Mean ciprofloxacin pharmacokinetic parameters from phase 1 (without calcium) and phase 2 (with calcium) for compartmental and noncompartmental models

Parameter and phase	Mean (SD)		% Difference between phase 1 and phase 2		P	
	Compartmental (n = 10)	Noncompartmental (n = 12)	Compartmental (n = 10)	Noncompartmental (n = 12)	Compartmental (n = 10)	Noncompartmental (n = 12)
C_{max} (mg/liter)						
1	1.25 (0.24)	1.98 (0.43)	13	18	0.000036	0.039
2	1.44 (0.34)	2.42 (0.47)				
T_{max} (h)						
1	2.56 (0.86)	1.82 (0.60)	22	45	0.12	0.038
2	2.10 (0.73)	1.26 (0.41)				
$t_{1/2\beta}$ (h)						
1	3.19 (0.76)	4.02 (0.70)	11	6	0.18	0.48
2	2.88 (0.63)	3.80 (0.99)				
k_{el} (h^{-1})						
1	0.23 (0.05)	0.18 (0.03)	5	9	0.32	0.29
2	0.22 (0.04	0.20 (0.05)				
AUC_{0-12}[a] (mg · h/liter)						
1	8.84 (1.55)	9.85 (1.59)	2	3	0.40	0.68
2	9.05 (1.86)	10.14 (1.80)				
$AUC_{0-\infty}$ (mg · h/liter)						
1	10.24 (2.13)	11.58 (2.15)	2	0.25	0.42	0.97
2	10.03 (2.33)	11.55 (2.56)				
F	1.03	0.98				

[a] AUC_{0-12} is the area up to the last measured concentration in serum.

type of dosing in the clinical setting, and further studies in this area are warranted.

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REFERENCES

1. **Anonymous.** 1990. Calcium drug evaluation monograph, vol. 65. Drugdex, Micromedex Inc., Denver.
2. **Bianchi, W., F. Maggiolo, A. Imbasciati, and H. K. P. Ohnmeiss.** 1988. Antacids and ciprofloxacin pharmacokinetics. Antimicrob. Agents Chemother. **32**:949.
3. **Crump, B., R. Wise, and J. Dent.** 1983. Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob. Agents Chemother. **24**:784–786.
4. **Fleming, L. W., T. A. Moreland, W. K. Stewart, and A. C. Scott.** 1986. Ciprofloxacin and antacids. Lancet **ii**:294.
5. **Frost, R. W., J. T. Lettieri, A. Noe, E. C. Shamblen, and K. Lasseter.** 1989. Effect of aluminum hydroxide and calcium carbonate antacids on ciprofloxacin bioavailability. Clin. Pharmacol. Ther. **45**:165.
6. **Hoffken, G. K., K. Borner, P. D. Glatzel, P. Koeppe, and H. Lode.** 1985. Reduced enteral absorption of ciprofloxacin in the presence of antacids. Eur. J. Clin. Microbiol. **4**:345.
7. **Ivanovich, P., H. Fellows, and C. Rich.** 1967. The absorption of calcium carbonate. Ann. Intern. Med. **66**:917–923.
8. **Joos, B., B. Ledergerber, M. Flepp, J. D. Bettex, R. Luthy, and W. Siegenthaler.** 1985. Comparison of high-pressure liquid chromatography and bioassay for determination of ciprofloxacin in serum and urine. Antimicrob. Agents Chemother. **27**:353–356.
9. **Kobrin, S. M., S. J. Goldstein, R. F. Shangraw, and R. M. Raja.** 1989. Variable efficacy of calcium carbonate tablets. Am. J. Kidney Dis. **14**:461–465.
10. **Lomaestro, B. M., and T. S. Lesar.** 1989. Concurrent administration of ciprofloxacin and potentially interacting drugs. Am. J. Hosp. Pharm. **46**:1770.
11. **Miles, Inc., Pharmaceutical Division.** 1987. Ciprofloxacin package insert. Miles, Inc., West Haven, Conn.
12. **Nix, D. E., W. A. Watson, L. Handy, W. Frost, D. L. Rescott, and H. R. Goldstein.** 1989. The effect of sucralfate pretreatment on the pharmacokinetics of ciprofloxacin. Pharmacotherapy **9**:377–380.
13. **Nix, D. E., J. H. Wilton, J. J. Schentag, H. P. Salvinaz, A. Norman, and H. R. Goldstein.** 1989. Inhibition of norfloxacin absorption by antacids and sucralfate. Rev. Infect. Dis. **11**(Suppl. 5):S1096.
14. **Parpia, S. H., D. E. Nix, L. G. Hejmanowski, H. R. Goldstein, J. H. Wilton, and J. J. Schentag.** 1989. Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob. Agents Chemother. **33**:99–102.
15. **Plaisance, K. I., G. L. Drusano, A. Forrest, C. I. Bustamante, and H. C. Standiford.** 1987. Effects of dose size on bioavailability of ciprofloxacin. Antimicrob. Agents Chemother. **31**:956–958.
16. **Polk, R. E., D. P. Healy, J. Sahai, L. Drwal, and E. Racht.** 1989. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. Antimicrob. Agents Chemother. **33**:1841–1844.
17. **Rubenstein, E., and S. Segev.** 1987. Drug interactions of ciprofloxacin with other non-antibiotic agents. Am. J. Med. **82**(Suppl. 4A):119–123.
18. **Sahai, J., D. Healy, J. Stotka, and R. Polk.** 1989. Influence of chronic administration of calcium (CA) on the bioavailability (BA) of oral ciprofloxacin (CIP). Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 211.
19. **Terp, D. K., and M. J. Rybak.** 1987. Ciprofloxacin. Drug. Intell. Clin. Pharm. **21**:568–574.