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Relative Bioavailability in Healthy Volunteers of Ciprofloxacin Administered through a Nasogastric Tube with and without Enteral Feeding

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The bioavailability of ciprofloxacin after its administration through a nasogastric (NG) feeding tube was studied in six healthy volunteers. Each subject received, on separate occasions, an intact 750-mg ciprofloxacin tablet, a crushed tablet as a suspension through an NG tube, and a crushed tablet as a suspension through an NG tube while receiving enteral feeding. No statistically significant differences were observed in the area under the curve, maximum concentration in serum, and time to peak concentration among these three modes of administration. These findings suggest that ciprofloxacin is well absorbed after administration via an NG tube (compared with an orally administered intact tablet) even in the presence of enteral feeding.

Ciprofloxacin is often considered for patients who would otherwise require parenteral antibiotics because of its potent antimicrobial activity, high tissue penetration characteristics, and lack of cross resistance with other groups of antibiotics. Patients with serious infections who are clinically unstable, however, often cannot maintain adequate intake by mouth and, therefore, require drugs to be administered parenterally or via nasoenteric tubes. Although ciprofloxacin has been administered through a nasogastric (NG) tube in clinical practice, the extent of absorption via an NG tube and the effect of enteral feeding on the bioavailability are not known. The bioavailability of ciprofloxacin has been reported to be approximately 70%, with peak concentrations in serum usually achieved 1 h after the dose (1, 2, 9–11). Food has been shown to delay the absorption of ciprofloxacin, but the overall extent of absorption is not affected (8). The absorption of ciprofloxacin has been shown to be decreased with the concurrent use of antacids (3, 6). In view of the importance of ensuring adequate drug concentrations for the treatment of serious infections and the need for the exploration of the effect of different modes of administration on bioavailability, a study was conducted to determine the effect of administering ciprofloxacin through an NG tube with and without concurrent enteral feeding.

Six healthy male volunteers (mean age, 32 ± 5 years; mean weight, 72.7 ± 6.9 kg; mean height, 174.5 ± 2.7 cm) were selected after a physical examination and laboratory tests. Subjects did not have any significant history of gastrointestinal disease or surgery. Informed consent was obtained from each subject before the enrollment. No medication was allowed for 1 week prior to the administration of the study drug, and no consumption of alcohol or caffeine was allowed for 48 h prior to and for the duration of the study.

A randomized, three-way crossover study design was used such that each subject could eventually receive all three treatments. The treatments consisted of (i) an intact ciprofloxacin tablet taken orally, (ii) a crushed tablet suspension administered through an NG tube, and (iii) a crushed tablet suspension administered through an NG tube with concurrent enteral feeding. A 1-week washout followed each treatment.

When the intact tablet was given, a 750-mg ciprofloxacin tablet (lot no. TBIF7; Miles Inc.) was administered with 180 ml of water following an overnight fast.

For administration through the NG tube without feeding, a lubricated nasogastric feeding tube (size, 8 fr; length, 36 in. [ca. 91.4 cm]; a small-bore, flexible catheter; Corpak Co.) was swallowed by the volunteers as instructed under the supervision of a physician at least 30 min before the administration of the drug. The proper positioning was checked by listening for the release of air into the stomach. A 750-mg ciprofloxacin tablet was crushed with a mortar and pestle, and the dry powder was suspended in 50 ml of water. After a gentle mixing, the content was taken up into a syringe and delivered through the NG tube over 1 min. An additional 65 ml of water was used twice to rinse any remaining drug and administered to the subject to ensure the delivery of the entire dose.

When ciprofloxacin was given through the NG tube with enteral feeding, the NG tube was placed in the same manner and enteral feeding (full-strength Osmolite) was delivered by an Imed pump at a rate of 100 ml/h for 2 h prior to the administration of the drug. Ciprofloxacin was prepared and delivered in the same way as previously described, and the enteral feeding was immediately resumed and continued for another 4 h postdose. After the collection of the 4-h sample, the NG tubes were removed. All the subjects remained in a sitting position during the first 4 h and refrained from physical exercise throughout the study. A standard lunch was provided 4 h postdose.

Blood samples were obtained before each dose (blank) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 h after dosing. Samples were allowed to clot, and serum was separated and stored frozen at −70°C until the time of assay.

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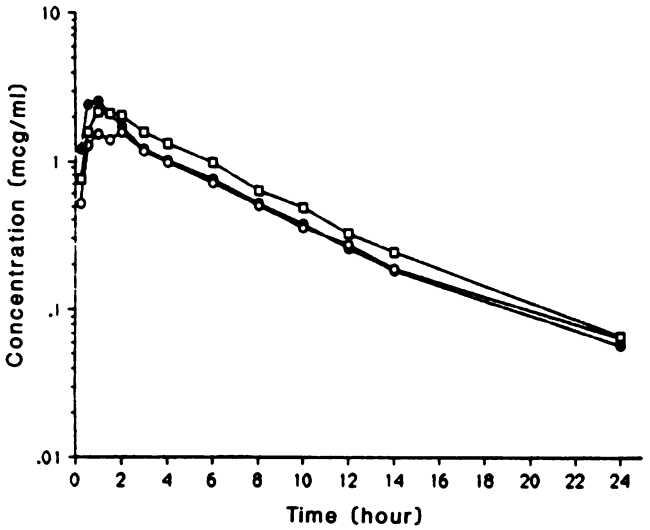

FIG. 1. Mean serum concentration-time curves after the administration of a single 750-mg ciprofloxacin dose as an intact tablet (●), a crushed tablet administered through an NG tube (○), and a crushed tablet via an NG tube with concurrent enteral feeding (□).

Ciprofloxacin concentrations were measured at Miles Inc. by using a high-performance liquid chromatographic assay previously described (7).

The area under the concentration-time curve in serum from time zero to infinity ($AUC_{0-\infty}$) was estimated by using the trapezoidal rule plus the quotient calculated by dividing the last measured concentration by the terminal elimination rate constant. The terminal elimination rate constant was obtained by performing a regression of the terminal phase of the data. The peak concentration (C_{max}) was determined by visual inspection, and the time to peak (T_{max}) was determined as the corresponding time for the peak concentration. The area under the moment curve (AUMC) was calculated by the trapezoidal rule and extrapolation methods (5), and mean residence time was calculated as $AUMC_{0-\infty}/AUC_{0-\infty}$. The pharmacokinetic parameters AUC, C_{max}, and T_{max} were compared statistically by using a univariate analysis of variance, as well as a two one-sided t test. The mean serum concentration-time curves are shown in Fig. 1.

All the subjects completed the study without any adverse effects. Subjects did not complain of any significant discomfort with the presence of feeding tubes of the size used in our study. Pharmacokinetic data obtained in this study are presented in Table 1.

There was no statistically significant difference among these three modes of administration in AUC ($P = 0.3983$), C_{max} ($P = 0.1903$), and T_{max} ($P = 0.3539$) as determined by analysis of variance ($P < 0.05$ was considered significant). However, confidence intervals, calculated by using a two one-sided t test for comparison of the intact tablet versus crushed tablet suspension through an NG tube and the intact tablet versus crushed tablet suspension through an NG tube with enteral feeding, were 52 to 122% and 79 to 149%, respectively, for the AUC; 76 to 279% and 65 to 268%, respectively, for T_{max}; and 48 to 104% and 76 to 132%, respectively, for C_{max}. Although these results are outside of the 80 to 120% range, they are consistent with the analysis of variance in that the differences between the groups are not significant. These results are probably due to the small number of subjects studied and relatively large variation in individual data as expected with oral administration of a single, fixed dose. However, this degree of difference observed is clinically insignificant.

TABLE 1. Mean pharmacokinetic parameters (plus or minus standard deviation)

Treatment[a]	$AUC_{0-\infty}$ (μg · h/ml)	T_{max} (h)	C_{max} (μg/ml)	$t_{1/2}$[b] (h)	MRT[c] (h)
A	13.17 ± 4.81	0.75 ± 0.27	2.80 ± 0.94	3.41	6.13
B	11.46 ± 4.51	1.33 ± 0.52	2.12 ± 0.37	3.77	6.80
C	15.02 ± 3.79	1.25 ± 0.94	2.92 ± 0.78	2.90	6.30

[a] Treatments: A, administration of intact ciprofloxacin tablet orally; B, administration of a crushed ciprofloxacin tablet as a suspension through an NG tube; C, administration of a crushed ciprofloxacin tablet as a suspension through an NG tube in the presence of enteral feeding.
[b] $t_{1/2}$, Harmonic mean of half-lives in serum.
[c] MRT, Mean residence time.

The appropriate utilization of a potent oral antibiotic such as ciprofloxacin for the treatment of infections which would otherwise require parenteral antibiotics can lead to a sizable cost savings with an equivalent therapeutic outcome. In the intensive care setting, various drugs are crushed and administered through NG tubes without adequate bioavailability data. In the absence of information on the effect of concurrent enteral feeding on the absorption of the drug, enteral feeding is often interrupted prior to drug administration and then resumed with the hope of avoiding possible drug-food interactions. This appears to be an unnecessary precaution, at least for ciprofloxacin, on the basis of the information obtained in this study. Only six subjects were included in this study, and one can argue that if the study was conducted with a large number of subjects, differences might have appeared. The magnitude of the differences observed in the present study is not likely to be clinically significant. In fact, the concurrent administration of enteral feeding showed not only a lack of interference but also a potential to enhance the overall absorption of ciprofloxacin. This finding is particularly interesting since the enteral feeding formula contains magnesium (21.1 mg of Mg per 100 ml of Osmolite), which has been implicated in reduced absorption of ciprofloxacin. To date, no studies have clearly demonstrated a decreased absorption of ciprofloxacin with the use of magnesium alone. All reported interactions (3, 6) involved antacids which contain aluminum, and it is possible that it is only this ion that interacts with ciprofloxacin. Even if a magnesium-ciprofloxacin interaction occurs, it may not be evident after enteral feeding since a relatively small amount of magnesium is provided in a large volume of fluid over a long period of time. The degree of interaction reported with calcium is much lower (3, 4). Even if it occurs, such an interaction would not be noted in this study for the same reason. The absence of an interaction in this study, even with the ability of enteral feeding to neutralize gastric pH to some degree, further implies that the interactions reported with antacids are probably due to chelate formation rather than to the change in pH. Whether a degree of drug concentrations similar to that observed in our normal volunteer study could be achieved in critically ill patients needs further investigation.

Our finding provides a rationale for the administration of ciprofloxacin via an NG tube to patients who cannot take an intact tablet. Furthermore, it suggests that concurrent enteral feeding does not interfere with the absorption of ciprofloxacin and, thus, does not have to be interrupted when administering ciprofloxacin.

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