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Ciprofloxacin Absorption Is Impaired in Patients Given Enteral Feedings Orally and via Gastrostomy and Jejunostomy Tubes

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Twenty-six hospitalized patients participated in a randomized crossover study to evaluate the effect of enteral feedings on ciprofloxacin absorption when given orally or via gastrostomy or jejunostomy tubes. Patients in the oral group received an intact 500-mg ciprofloxacin tablet alone or ciprofloxacin plus three oral doses of Sustacal (240 ml given 8 h before, with, and 4 h after ciprofloxacin administration). Patients with gastrostomy or jejunostomy tubes received 500 mg of crushed ciprofloxacin in 60 ml water via the feeding tube. After a washout period, the patients received ciprofloxacin with a continuous enteral formula (Jevity) given at 60 to 90 ml/h beginning 6 h before drug administration and continuing for 10 h. Serial blood samples were analyzed for ciprofloxacin concentration by high-performance liquid chromatography. The maximum ciprofloxacin concentrations in serum for ciprofloxacin given and for ciprofloxacin plus enteral feeding for the oral, gastrostomy, and jejunostomy groups were (mean ± standard deviation) 2.59 ± 1.24 versus 1.43 ± 0.61 μg/ml ($P < 0.05$), 3.68 ± 1.36 versus 2.27 ± 0.67 μg/ml ($P < 0.05$), and 3.78 ± 1.87 versus 1.45 ± 0.48 μg/ml ($P < 0.05$), respectively. Corresponding values for area under the concentration-time curve were 13.4 ± 8.32 versus 9.44 ± 4.74 μg/h/ml ($P < 0.05$) 15.9 ± 6.62 versus 7.44 ± 3.16 (μg/h/ml ($P < 0.05$), and 18.1 ± 9.37 versus 5.82 ± 2.63 μg · h/ml ($P < 0.05$). We conclude that enteral feedings given orally or via gastrostomy or jejunostomy tubes resulted in a 27 to 67% reduction in the mean bioavailability of ciprofloxacin in hospitalized patients. The decreased absorption may be clinically important, especially when the enteral feeding is coadministered with ciprofloxacin by the oral and jejunostomy tube routes. Reductions in maximum levels of ciprofloxacin in serum as a result of feedings given via a gastrostomy tube are similar to those following oral administration on an empty stomach, making a clinically important interaction by this route less likely.

Single doses of ciprofloxacin are rapidly absorbed, with an absolute bioavailability averaging between 69 and 85% (7). Administration of ciprofloxacin with food, while delaying the time to maximum concentration (T_{max}), does not significantly alter the maximum concentration of the drug in serum (C_{max}) or the overall extent of drug absorption (14). It is well known that the absorption of all quinolones is impaired by aluminum-magnesium antacids, sucralfate, calcium, and various mineral supplements (iron, zinc) (5, 12, 21). Commonly used enteral feeding products contain various amounts of these cations and are often given concomitantly with quinolones as an oral bolus supplement or as a continuous feeding through a gastrostomy tube (g-tube) or jejunostomy tube (j-tube) for total enteral nutrition.

Four studies have evaluated the influence of enteral feedings on quinolone bioavailability (16, 19, 27, 28), but most suffer from one or more of the following limitations: small sample size combined with noncrossover design (27), use of healthy volunteers instead of hospitalized patients (16, 19, 28), and failure to use a feeding tube (16, 19). The only study performed with patients that evaluated the effect of enteral feedings on quinolone bioavailability via a feeding tube was performed with a relatively small and heterogeneous study sample of seven patients (27). These authors found that for the four patients with a nasoduodenal (ND) tube who were receiving Jevity, the mean area under the curve (AUC) for ciprofloxacin was higher than for the three patients receiving the drug via a nasogastric (NG) tube or g-tube. Different rates of enteral feeding administration, a bias toward more elderly patients with ND tubes, large interpatient variability, the lack of a crossover design, and the use of a historical healthy volunteer control group make the results inconclusive.

The purpose of the present study was to determine the effect of a typical enteral supplement (Sustacal) given as multiple intermittent oral boluses on the bioavailability of an intact dose of oral ciprofloxacin in hospitalized patients. The second aim was to determine the effect of a common enteral nutritional formula (Jevity) given as a continuous-rate feeding on the absorption of a crushed dose of ciprofloxacin administered through a g-tube or a j-tube in patients.

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MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Boards of the University of Cincinnati (a tertiary-care medical center) and The Drake Center, Inc. (a long-term subacute care and rehabilitation hospital).

Patients. Twenty-six adult, stable, hospitalized patients within 30% of their ideal weight, who were not in the intensive care unit, gave informed consent and were enrolled in the study. Ten patients received their enteral nutrition orally, while the other 16 received their total nutrition via a surgically placed feeding tube (10 via a g-tube, and 6 via a j-tube). Patients were excluded if they had a known or suspected malabsorption state, recent intra-abdominal surgery, previous partial gastrectomy or removal of a significant portion of small or large bowel, renal insufficiency with estimated creatinine clearance < 40 ml/min, changing renal or hepatic function, or ascites or were receiving theophylline, warfarin, cyclosporin, phenytoin, phenobarbital, erythromycin, rifampin, metoclopramide, Imodium, Lomotil, or other quinolone within five elimination

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TABLE 1. Group demographics for patients given ciprofloxacin with and without enteral feedings via the oral, g-tube, and j-tube routes

Treatment group[b] (no. of patients)	Sex[a]	Age (yr)	Wt (kg)	Scr (mg/dl)[b]	Rate of tube feeding (ml/h)
Oral (n = 10)	8m, 2f	51.2 ± 15.3 (27–71)	84.3 ± 20.3 (47.9–118)	0.8 ± 0.3 (0.4–1.5)	NA[c]
g-tube (n = 10)	7m, 3f	47.5 ± 19.5 (20–86)	67.1 ± 11.9 (47.5–81.8)	0.7 ± 0.2 (0.5–0.9)	75.5 ± 7.62 (60–90)
j-tube (n = 6)	4m, 2f	60.7 ± 15.8 (43–80)	74.1 ± 5.2 (67.7 ± 80.5)	0.7 ± 0.2 (0.4–0.9)	80.8 ± 7.36 (75–90)

[a] Abbreviations: m, male; f, female.
[b] Scr, serum creatinine. Refer to text for a detailed description of treatment regimens.
[c] NA, not applicable. Data are means ± standard deviations (range).

half-lives of study entry. Females of child-bearing potential were excluded if they had a positive urine pregnancy test. Patients receiving antacids, sucralfate, iron, or other di/trivalent cations were enrolled only if their doses could be held for a minimum of 6 h before and 4 h after each ciprofloxacin dose (18).

Drug administration and sample collection. A randomized, two-period, two-treatment, two-sequence crossover design was used for each of the three patient groups. After an overnight fast, patients in the oral group randomly received a single intact tablet of ciprofloxacin (500 mg; Cipro [lot 1FBU]; Pharmaceutical Division, Miles, Inc., West Haven, Conn.) with 240 ml of water or with three intermittent oral doses of enteral formula (240 ml; ready-to-use vanilla flavor Sustacal [lot 03519B073]; Mead Johnson, Evansville, Ind.) given 8 h before, concomitantly with, and 4 h after ciprofloxacin dosing. Patients were given a standard lunch 5 h after ciprofloxacin dosing. Patients with g- or j-tubes each received a 500-mg ciprofloxacin tablet crushed in a glass mortar, with the dry powder suspended in 60 ml of distilled water and given via their feeding tube. Two additional 30-ml volumes of water, rinsed through the mortar, were used to ensure total drug delivery and to rinse the tubing. After a 3-day washout period, patients received ciprofloxacin in the same manner with a continuous enteral feeding formula (Jevity ready-to-use [lot 02162RNO-61]; Ross Laboratories, Columbus, Ohio) delivered by a Ross Companion pump at a rate of 60 to 90 ml/h beginning at least 6 h before drug administration and continuing for an additional 4 h (minimum) after dosing. The rate of enteral formula administration for each patient was the same on both study days. Serial blood samples for ciprofloxacin concentrations in serum were collected before drug administration on each study day and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after dosing. Serum samples were stored frozen at −80°C until the time of assay.

Ciprofloxacin assay. Ciprofloxacin concentrations were measured in our laboratory by a modification of the reversed-phase high-performance liquid chromatography plus fluorescence detection method of Nix et al. (17). The only differences included a mobile phase consisting of 13% acetonitrile and 87% phosphate buffer (pH 3.0) and the incorporation of an extraction step with a C_{18} solid-phase extraction cartridge (Supelclean LC-18 SPE; Supelco, Inc., Bellefonte, Pa.). The cartridge was fitted to the top of a vacuum manifold under a pressure of about 250 mm Hg. The cartridge was primed with three 1-ml volumes of methanol followed by 1 ml of phosphate buffer (20 mM) adjusted to pH 12 with 4 M sodium hydroxide. A 500-μl volume of unknown sample, standard, or control containing the internal standard (difloxacin; Abbott Laboratories, North Chicago, Ill.) was then added, followed by 1 ml of Millipore water and 500 μl of methanol. The effluent was discarded. The sample was then eluted into a collection vial with 1 ml of acidified methanol (4 parts glacial acetic acid plus 50 parts methanol), evaporated to dryness under nitrogen, and reconstituted with 500 μl of the mobile phase. A 10-μl injection volume was assayed in duplicate. Quantification was performed by comparison of the sample peak area ratios (peak area of drug divided by peak area of internal standard) with the standard curve. High (2.5 μg/ml), medium (0.625 μg/ml), and low (0.156 μg/ml) control samples were placed between every seven unknown specimens.

The range of assay linearity was from 0.078 to 5.0 μg/ml. All standard curves had a correlation coefficient of >0.99. The lower limit of detection was 0.078 μg/ml; this represents a signal-to-noise ratio of 4. The between-day and within-day coefficients of variation for the control values were <8%. Control values deviating from theoretical values by more than 25% were considered out of range, and bracketed unknown samples were reassayed.

Data and statistical analysis. The maximum concentration (C_{max}) of ciprofloxacin in serum and the time to reach C_{max} (T_{max}) were determined directly from the individual data. The terminal elimination rate constant (λ_z) was obtained by least-squares regression of the log drug concentrations in serum in the log-linear phase. The last six log concentration-time points for each regimen were used to represent the log-linear phase. Least-squares linear regression of these data indicated correlation coefficients of >0.99. The elimination half-life ($t_{1/2}$) was calculated by dividing 0.693 by λ_z. The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) for 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. The segment of total AUC that was extrapolated to infinity averaged 8.1% (standard deviation 5.5%). Relative bioavailability was calculated as the ratio (drug with enteral feed $AUC_{0-\infty}$)/(drug with water $AUC_{0-\infty}$).

Differences in mean pharmacokinetic parameters of ciprofloxacin between treatments were evaluated by an analysis of variance model appropriate for a crossover design (15). The Wilcoxan rank sum test appropriate for a two-period, two-sequence crossover design was used to compare the median values for T_{max} (11). All pharmacokinetic parameters except T_{max} and $t_{1/2}$ were logarithmically transformed. The least-squares geometric and arithmatic means were used in the analysis of variance calculations. Effects of treatment and period were tested by the mean-square residual, and the effects of sequence were tested by the patient-within-sequence mean-square term. Intrasubject coefficient of variation (CV) and power were calculated as previously described (8). Statistical significance was defined as $P < 0.05$. On the basis of our previously published studies involving absorption interferences of quinolones (22, 24), a prestudy power analysis indicated that a sample size of 10 per group (with a crossover design) would yield >80% power (probability) of detecting a ≥30% change in C_{max} or AUC at the 5% level of significance (3, 25). Results are expressed as means ± standard deviations, with the exception of T_{max} values, which are given as median (range).

RESULTS

Twenty-six patients or their legal surrogates gave informed consent. All patients completed the study. The demographics of the three patient groups are shown in Table 1. There were no adverse effects reported by the patient or nursing personnel.

The pharmacokinetic parameters for the three groups are listed in Table 2. The mean serum concentration-versus-time profiles, with and without the influence of the enteral feedings, are graphically depicted in Fig. 1. Enteral feedings decreased the mean C_{max} by 43, 37, and 59% in the oral, g-tube, and j-tube groups, respectively. The corresponding AUC values were decreased by 27, 53, and 67%. As expected, the median T_{max} was delayed in the oral group receiving the enteral feeding (3.0 h; range, 1.0 to 6.0 h) compared with ciprofloxacin alone on an empty stomach (1.0 h; range, 0.5 to 2.0 h; $P < 0.05$). The $t_{1/2}$ of ciprofloxacin was not significantly altered by coadministration of enteral feedings via any route.

This study had 80% power at the 5% level of significance to detect a 28% decrease in C_{max} and a 25% decrease in $AUC_{0-\infty}$ in the oral group relative to the values for reference ciprofloxacin alone (Table 2). Corresponding differences of 24 and 29% could be detected in the g-tube group with 80% power. The intrasubject variability was greater in the j-tube group for C_{max} (43% CV) and $AUC_{0-\infty}$ (38% CV). This resulted in the ability to detect only differences greater than 40% in C_{max} and 44% in $AUC_{0-\infty}$ with 80% power. However, the actual mean decrease in these parameters relative to reference ciprofloxacin alone was 59 and 67%, respectively.

DISCUSSION

The use of oral fluoroquinolones in medical practice continues to increase. This is due in part to an increase in infections caused by multidrug-resistant organisms against which the quinolones are active (13). More notable, perhaps, is the use of these potent agents in an effort to change from an expensive parenteral regimen to a more cost-effective oral agent for outpatient administration in selected patients (4). An underlying assumption in establishing equal efficacy between follow-up quinolone therapy and continued parenteral therapy is that the

TABLE 2. Mean pharmacokinetic parameters of ciprofloxacin administered alone and with enteral feedings by the oral, g-tube, and j-tube routes[a]

Route	Parameter	Value with treatment:		ANOVA for crossover design				
		Ciprofloxacin alone	Ciprofloxacin plus feeding	%Δ[b]	90% confidence limits	*P*	Intra-subject % CV	$\%\Delta_{80\%}$[c]
Oral	C_{max} (μg/ml)	2.59 ± 1.24	1.43 ± 0.61	−42.9	−52.9, −30.7	0.0006	23.2	−28.2
	t_{max} (h)[d]	1.0 (0.5, 2.0)	3.0 (1.0, 6.0)	1.50	1.00, 2.75	<0.05	50.3	71.9
	$AUC_{0-\infty}$ (μg · h/ml)	13.4 ± 8.32	9.44 ± 4.74	−27.2	−38.3, −14.0	0.007	20.0	−24.8
	$t_{1/2}$ (h)	4.16 ± 1.20	4.12 ± 1.42	−2.64	−18.8, 16.7	0.791	21.8	−26.8
g-tube	C_{max} (μg/ml)	3.68 ± 1.36	2.27 ± 0.67	−37.3	−48.6, −23.4	0.002	24.0	−29.0
	t_{max} (h)[d]	1.0 (0.5, 1.5)	0.5 (0.5, 1.5)	−1.49	−1.86, −0.68	<0.05	25.6	−36.5
	$AUC_{0-\infty}$ (μg · h/ml)	15.9 ± 6.62	7.44 ± 3.16	−53.0	−59.8, −45.0	0.00002	18.8	−23.5
	$t_{1/2}$ (h)	3.37 ± 1.22	2.80 ± 1.14	−17.6	−31.9, −0.29	0.096	23.0	−28.0
j-tube	C_{max} (μg/ml)	3.78 ± 1.87	1.45 ± 0.48	−59.3	−76.0, −31.1	0.022	42.8	−39.9
	t_{max} (h)[d]	0.5 (0.5, 1.5)	1.0 (0.5, 1.0)	0.00	−0.25, 0.50	0.643	36.5	78.3
	$AUC_{0-\infty}$ (μg · h/ml)	18.1 ± 9.37	5.82 ± 2.63	−66.5	−79.0, −46.4	0.007	38.1	−44.2
	$t_{1/2}$ (h)	3.44 ± 1.04	3.10 ± 1.47	−13.6	−34.9, 14.7	0.333	23.0	−39.0

[a] A 500-mg single dose of ciprofloxacin and three doses of an oral enteral feed (Sustacal) given as 240 ml 8 h before, concomitantly with, and 4 h after ciprofloxacin administration or Jevity given by continuous-rate infusion (60 to 90 ml/h) via g- or j-tube beginning 6 h before ciprofloxacin administration and continuing for an additional 4 h after dosing. Values are arithmatic means ± standard deviations, except for t_{max} values, which are medians (with minimum and maximum given in parentheses).

[b] Percent change of the least-squares geometric treatment mean (C_{max}, AUC) or the least-squares arithmatic treatment mean (t_{max}, $t_{1/2}$) of the ciprofloxacin-plus-enteral-feeding treatment relative to the ciprofloxacin-alone treatment. The value for t_{max} is the point estimate of the absolute difference of expected medians, relative to the ciprofloxacin-alone treatment. A negative value refers to a decrease.

[c] Percent change of the least-squares means (see footnote *b*) that can be detected with 80% power at the 5% level of significance.

[d] Analyzed by the nonparametric rank sum test.

oral bioavailability of the quinolone is unaffected by coadministration with food or other medications. Administration of quinolones with food, while delaying the T_{max}, generally does not alter the C_{max} or AUC (14). The reduction in quinolone absorption by commonly used products such as antacids, sucralfate, calcium-containing products, iron, and other cationic substances has been documented by numerous studies (5, 9, 12, 21–24, 26). In addition, the potential for treatment failure as a result of decreased oral quinolone bioavailability, requiring extended and costly parenteral therapy, has been documented in at least one published case report (20).

Commonly used enteral feeding products contain different amounts of divalent cations and are often given concomitantly with quinolones as an intermittent oral bolus supplement or as a continuous feeding through a g- or j-tube for patients receiving total enteral nutrition (unpublished data).

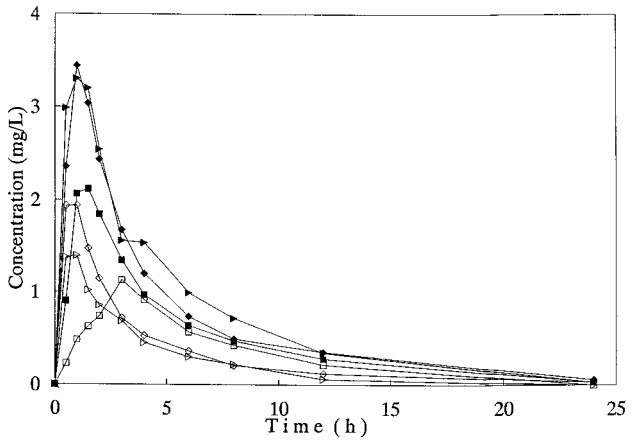

FIG. 1. Mean ciprofloxacin concentrations in serum after a single 500-mg dose given orally (□, ■) via g-tube (◇, ◆) or via j-tube (▷, ▶) each with (open symbols) and without (solid symbols) the presence of enteral feedings.

Four studies have evaluated the influence of enteral feedings on quinolone bioavailability (16, 19, 27, 28); however, most were conducted with young healthy volunteers and/or did not assess the use of enteral feeding tubes (16, 19, 28). Two studies investigating the effects of three different oral enteral feeding supplements in normal healthy volunteers have shown a significant reduction in ciprofloxacin bioavailability (16, 19). Pulmocare, Osmolite, and Ensure (all from Ross Labs.) reduced the C_{max} of ciprofloxacin by 30, 26, and 47%, respectively. The corresponding relative bioavailabilities (AUCs) were reduced to 67, 58, and 72% of their control values (e.g., without enteral supplements). Data from the present study in patients receiving Sustacal (oral group) were similar, with a mean (90% confidence interval) reduction in the C_{max} of 43% (31 to 53%) and a mean reduction in the relative bioavailability of 73% (62 to 86%) with respect to control values. The overall reductions were similar for all four enteral products despite different cation contents in the formulas. For example, the amounts of calcium, magnesium, zinc, iron, and copper in Pulmocare (250, 100, 5.57, 4.50, and 0.38 mg, respectively) and Sustacal (240, 90, 3.30, 4.00, and 0.47 mg) are roughly twice those in Osmolite and Ensure (both contain 125, 50, 2.82, 2.25, and 0.25 mg, respectively), yet reductions in C_{max} and AUC were similar for all four. This may be attributed to different dosing methods used in different studies and/or to the possibility that mechanisms other than, or in addition to, chelation (e.g., adsorption) are operative with enteral formulas. Interestingly, the one volunteer study that did evaluate the effect of administration through an NG tube did not find a significant reduction in quinolone bioavailability as a result of the enteral feeding (28). However, given the reported large intersubject variability and small sample size, the authors were accurate in noting the low study power to detect a real difference. These data, taken together, indicate a reduction in ciprofloxacin bioavailability

when oral supplements were given concomitantly with ciprofloxacin. The clinical significance of this interaction for particular infections is unknown; therefore, the combination should be avoided until data delineating an optimal time frame of dose separation are available.

The only study performed with patients that evaluated the effect of enteral feedings on quinolone bioavailability via a feeding tube was done with a relatively small and heterogeneous study sample of seven patients (27). The authors reported that for four intensive care unit patients receiving Jevity via an ND tube, the mean AUC of ciprofloxacin (following 750 mg) was larger than for the three patients receiving the drug via an NG or g-tube (25.35 ± 8.28 versus 11.27 ± 5.39 μg · h/ml). They suggested that the relatively decreased absorption by the NG tube and g-tube routes was possibly due to degradation of ciprofloxacin in the gastric environment; however, no data supporting that hypothesis have been published. In addition to the small sample size, several confounding variables were present, including different rates of enteral feeding administration (60 to 100 ml/h) without a comparable crossover arm, a bias toward more elderly patients with ND tubes (74 ± 2.6 versus 61 ± 13.5 years), large interpatient variability (AUC, 48% CV), and the use of a historical healthy volunteer control group for comparison. As a result, the findings are inconclusive.

In the present trial, Jevity given by a constant-rate administration via a g- or j-tube reduced the mean (90% confidence interval) percent bioavailability of ciprofloxacin by 53% (45 to 60%) and 67% (46 to 79%), respectively. Thus, the overall impairment of quinolone absorption was greater for the tube-fed patients than for those in the oral group. Despite such a large percent reduction in C_{max} for the g-tube group, the reduced value (2.3 ± 0.69 μg/ml) was similar to that following oral administration of the intact tablet on an empty stomach (2.6 ± 1.2 μg/ml; $P > 0.05$). The most likely explanation for the greater C_{max} obtained by g-tube (and j-tube) administration without any influence of tube feedings may be related to the administration of what is essentially a bolus solution of ciprofloxacin delivered well within its overall window of absorption. An intact tablet, on the other hand, must undergo disintegration and dissolution before being absorbed. Thus, there are "preabsorption," absorption, distribution, metabolism, and elimination processes occurring simultaneously. This would obviously result in a blunted C_{max} relative to that obtained with a solution bolus (10).

Since the C_{max}-to-MIC ratio has been suggested to be an important pharmacodynamic response parameter of the concentration-dependent killing activity of quinolones (2, 6), enteral feedings interacting with ciprofloxacin by the g-tube route may not be clinically important. Another piece of data that loosely supports this possibility is that the 12-h trough concentrations following a single dose of 500 mg of ciprofloxacin (0.14 ± 0.11 μg/ml) would still be at or near the MIC at which 90% of the isolates are inhibited (MIC_{90}) for many susceptible gram-negative organisms (13). Theoretically, trough concentrations at steady state and/or higher dosages (750 mg) would yield even higher concentrations. On the other hand, however, the AUC following g-tube administration is significantly reduced by Jevity relative to the AUC for the oral tablet administered on an empty stomach (7.4 ± 3.2 versus 13.4 ± 8.3 μg · h/ml; $P < 0.05$). Since the area under the bactericidal activity curve (AUBC) has also been suggested to be an important patient-specific parameter, integrating antibiotic pharmacokinetics and microorganism dynamics (1). Therefore, the overall clinical significance of this pharmacokinetic interaction by the g-tube route is unknown.

The mean (and 90% confidence interval) reductions in C_{max} and AUC of ciprofloxacin when administered by the less commonly used j-tube route, in the presence of continuous enteral feedings, are 59% (31 to 76%) and 67% (46 to 79%), respectively. This dramatic reduction in overall absorption is more likely to have negative clinical implications than is the interaction occurring by the g-tube route. Therefore, in the absence of data delineating the clinical relevance of this interaction or data indicating an optimal dose separation time, it would be prudent to use a nonquinolone agent when possible. While there are some data obtained with healthy volunteers to indicate that the reduction in bioavailability as a result of enteral feedings is smaller in magnitude with ofloxacin (16), the same guidelines should be applied for all quinolones until more specific data obtained with patients becomes available. The need to assess the clinical significance of this absorption interference will become increasingly important, especially as the concomitant use of quinolones and enteral feedings continues to grow in the subacute-care and long-term-care patient populations.

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