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Effect of Enteral Feeding with Ensure on Oral Bioavailabilities of Ofloxacin and Ciprofloxacin

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The relative oral bioavailabilities of ciprofloxacin and ofloxacin when they were coadministered with water or an enteral feeding product (Ensure) were assessed in 13 healthy volunteers. The area under the concentration time curve from time zero to infinity and the maximum concentration of drug in serum for both drugs were reduced by Ensure in comparison with those by water ($P < 0.01$). However, Ensure reduced the percent relative bioavailability of ciprofloxacin (72% ± 14%; range, 52 to 96%) significantly more than ofloxacin (90% ± 8.3%; range, 74 to 105%) ($P < 0.005$). Coadministration of Ensure significantly diminished ciprofloxacin and ofloxacin absorption, but ciprofloxacin absorption was reduced significantly more than ofloxacin absorption.

Fluoroquinolone antibiotics represent an important therapeutic advance in the treatment of bacterial infections. The beneficial characteristics of these agents include unique spectra of antimicrobial activity, favorable side effect profiles, and the advantages of both oral and parenteral routes of administration. Many serious infections which previously could be treated only with parenteral drugs can now be treated with an oral fluoroquinolone. The availability of oral fluoroquinolones has allowed more patients to be treated as outpatients and has expanded the use of oral antibiotics to the nursing home and critical care setting (49) to reduce drug costs (12, 31, 37).

The oral bioavailabilities of fluoroquinolone antibiotics may be affected adversely by interactions with divalent cations (1, 22, 35, 39, 41). Divalent cations contribute to the clinically important interactions of fluoroquinolone antibiotics with food (9, 15, 16, 18, 19, 27, 42, 43, 45), vitamins with iron (4, 17, 36), antacids (8, 14, 21, 28, 40, 41), and sucralfate (10, 32, 44). Of the two most studied fluoroquinolones, ciprofloxacin absorption appears to be affected more than ofloxacin absorption (6, 15, 26).

The reduced bioavailabilities of oral fluoroquinolone antibiotics because of drug interactions may be important, particularly in the critical care setting, because therapeutic failures have been reported (30, 38). The practice of using the enteral rather than the parenteral route to provide nutrition is becoming more common in intensive care units (ICUs) and nursing homes, where the provision of nutrition by the parenteral route is not always an option. The revised American Society of Parenteral and Enteral Nutrition Critical Care Practice Guidelines state that parenteral feeding should be instituted only when enteral feeding fails, is contraindicated, or enteral access cannot be obtained (2). Commercially available enteral feeding products may contain substantial amounts of divalent cations which may interact with oral fluoroquinolone antibiotics. Of the marketed fluoroquinolones, only ciprofloxacin's absorption when it is coadministered with enteral feeds has been studied (29, 47, 48). Those studies that used ciprofloxacin have yielded disparate results.

Because of the increasingly common practices of using oral fluoroquinolones and enteral feedings in ICU and nursing home settings, many patients may receive both of these therapies concurrently (23). We conducted a study to assess the influence that concomitant enteral feeding with an enteral feeding product (Ensure) has on the absorption of oral ciprofloxacin and ofloxacin.

MATERIALS AND METHODS

Protocol. Thirteen healthy adults gave informed consent and were enrolled in the study. Subjects were excluded if they were pregnant or were intending to become pregnant within 30 days of the conclusion of the study. Other exclusion criteria included breastfeeding at the time of the study and use of any medications during the 24 h prior to the study periods. Any known allergies to the fluoroquinolones, heparin, or the ingredients of Ensure also precluded participation. The study was approved by the Institutional Review Board at Indiana University and the Human Use Committee at Purdue University.

A randomized crossover design with four treatments was used. Each subject received all four treatments in random order. The treatments were (i) ofloxacin (400 mg; Floxin; Ortho Pharmaceutical Corporation, Raritan, N.J.) and water, (ii) ofloxacin (400 mg) and enteral feed (vanilla flavor; ready-to-use Ensure; Ross Laboratories, Columbus, Ohio), (iii) ciprofloxacin (750 mg; Cipro; Pharmaceutical Division, Miles Inc., West Haven, Conn.) and water, and (iv) ciprofloxacin (750 mg) and Ensure. A 1-week washout period was provided between each treatment.

Subjects fasted after 12:00 a.m. on each morning of the study days. At 6:00 a.m. subjects consumed 120 ml of study liquid (water or Ensure), which was repeated every 30 min for a total of five doses. With the second administration of study liquid, subjects ingested a single oral tablet of study drug (ciprofloxacin or ofloxacin) that had been uniformly crushed with a mortar and pestle and mixed into the study liquid. The cup with the crushed study drug was rinsed with an additional 60 ml of study liquid, which the subjects ingested, to ensure ingestion of the entire dose. The total dose of study liquid for each

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TABLE 1. Pharmacokinetic parameters[a]

Regimen	$AUC_{0-\infty}$ (mg · h/liter)	Relative bioavailability[b]	C_{max} (mg/liter)	T_{max} (h)	k_{el} (h^{-1})	Half-life (h)
Ciprofloxacin-Ensure	11.66 ± 3.70[c] (7.24–17.29)	0.72 ± 0.14[d] (0.52–0.96)	1.99 ± 0.57[c] (1.37–3.34)	2.42 ± 1.12[c] (1–4)	0.238 ± 0.043 (0.167–0.305)	3.00 ± 0.57 (2.27–4.15)
Ciprofloxacin-water	15.96 ± 3.12 (11.50–23.27)		3.79 ± 0.72 (2.18–5.07)	0.92 ± 0.19 (0.5–1)	0.243 ± 0.040 (0.180–0.334)	2.91 ± 0.46 (2.02–3.86)
Ofloxacin-Ensure	36.37 ± 9.98[e] (23.43–65.13)	0.90 ± 0.083 (0.74–1.05)	3.48 ± 0.84[c] (2.16–5.10)	2.04 ± 1.47[e] (0.5–6)	0.123 ± 0.031[e] (0.067–0.177)	6.00 ± 1.71[e] (3.92–10.36)
Ofloxacin-water	40.42 ± 11.01 (27.39–73.54)		5.47 ± 1.18 (3.13–7.39)	0.81 ± 0.69 (0.5–3)	0.136 ± 0.023 (0.090–.171)	5.25 ± 1.01 (4.05–7.71)

[a] Values are means ± standard deviations (ranges).
[b] Relative bioavailability measured as Ensure AUC/water AUC ratio.
[c] $P < 0.0005$ compared with the same drug taken with water.
[d] $P < 0.005$ compared with the other drug's relative bioavailability.
[e] $P < 0.05$ compared with the same drug taken with water.

treatment arm was 660 ml. No other food or drink was consumed within the first 4 h after the study drug was ingested.

Immediately prior to ingesting the study drug a baseline 5-ml blood sample was drawn from the subjects. Subsequent samples were drawn at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, and 24.0 h after the study drug was administered. Blood samples were obtained through a peripheral intravenous catheter placed by a study nurse. Blood samples were placed in a green-topped Vacutainer collection tube. Samples were centrifuged within 30 min of collection, frozen at −12°C, and transported on dry ice to a reference laboratory (Clinical Research Laboratory, Department of Pharmacy Practice, University of Illinois at Chicago) for analysis by reverse-phase high-performance liquid chromatography (HPLC).

Assay methodologies. The ofloxacin and ciprofloxacin HPLC assay methodologies were based on the method reported by Granneman and Varga (11). The only modification to the original procedure involved a change in the mobile phase composition from 53 to 42% (vol/vol) acetonitrile to improve the resolution of the assay. After the addition of a displacing reagent containing the internal standard (DNA gyrase inhibitor; A-57084; Abbott Laboratories, Abbott Park, Ill.), plasma samples were ultrafiltered with an Amicon Centrifree apparatus (Amicon Division, W. R. Grace & Co., Beverly, Mass.). The displacing reagent consisted of acetonitrile-water (30:70; vol/vol) containing 0.5% sodium dodecyl sulfate and 0.075 M phosphate. The ultrafiltrates were then injected into the HPLC system, which consisted of an Adsorbosphere HS C_{18} column (particle size, 7 μm; 4.6 by 250 mm; Alltech Associates, Deerfield, Ill. and a fluorescence detector (excitation, 280 nm; emission, 389 nm). The mobile phase consisted of acetonitrile-water (42:58; vol/vol) containing 0.04 M H_3PO_4, 0.01 M NaH_2PO_4, 0.04% sodium dodecyl sulfate, and 0.005 M *N*-acetylhydroxamic acid. Quantitation was determined by comparison of sample peak area ratios (peak area of drug divided by peak area of internal standard) with the standard curve.

The ciprofloxacin standard curves were linear in the range of concentrations between 0.0094 to 5.08 mg/liter. The intra-assay coefficient of variation for replicate samples within the concentration range of 0.0094 to 5.08 mg/liter was ≤2.68%. The interassay coefficient of variation was ≤3.27%. The minimum quantifiable plasma ciprofloxacin concentration was 0.0094 mg/liter.

The ofloxacin standard curves were linear in the range of concentrations between 0.0095 and 5.13 mg/liter. The intra-assay coefficient of variation for replicate samples within the concentration range of 0.0095 to 5.13 mg/liter was ≤3.07%. The interassay coefficient of variation was ≤2.51%. The minimum quantifiable plasma ofloxacin concentration was 0.0095 mg/liter.

Statistical procedures. The concentration-in-serum data were modeled with appropriate weights by using PCNONLIN. The curves generated from PCNONLIN were used to calculate the terminal half-life, elimination rate constant (k_{el}), and the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$). The maximum concentration in serum after the dose (C_{max}) and the time to reach C_{max} (T_{max}) were observed from the data for each patient. A paired *t* test was used to compare the mean C_{max}, T_{max}, and $AUC_{0-\infty}$ values for the individual drugs with and without enteral feedings. Relative bioavailability was calculated as the ratio of (drug with enteral feed $AUC_{0-\infty}$)/(drug with water $AUC_{0-\infty}$). A paired *t* test compared the mean percent relative bioavailabilities between the two drugs. Statistical significance was established at $P < 0.05$.

RESULTS

No modifications were made to the original study protocol. Thirteen healthy subjects (eight females, five males) gave informed consent and completed the study. The mean ± standard deviation age of the 13 study subjects was 30.54 ± 6.01 years. The mean subject weight was 75.27 ± 21.21 kg. No subject was required to drop from the study because of adverse effects.

The pharmacokinetic parameters for both drugs appear in Table 1. The $AUC_{0-\infty}$ of both drugs was significantly ($P < 0.005$) reduced with the coadministration of Ensure in comparison with that with the coadministration of water. However, Ensure reduced the percent relative bioavailability of ciprofloxacin (72% ± 14%; range, 52 to 96%) significantly more than it reduced that of ofloxacin (90% ± 8.3%; range, 74 to 105%) ($P = 0.0016$).

Ensure significantly lowered the C_{max} and lengthened the T_{max} for both drugs. The mean ciprofloxacin-Ensure C_{max} was 52.5% of the value for ciprofloxacin-water. Ofloxacin was less affected by Ensure. The mean ofloxacin-Ensure C_{max} was 63.6% of the ofloxacin-water C_{max}. As indicated in Table 1, the T_{max} for both drugs was prolonged by Ensure coadministration. ($P < 0.01$). The serum concentration-versus-time curves for both ciprofloxacin and ofloxacin appear in Fig. 1 and 2, respectively.

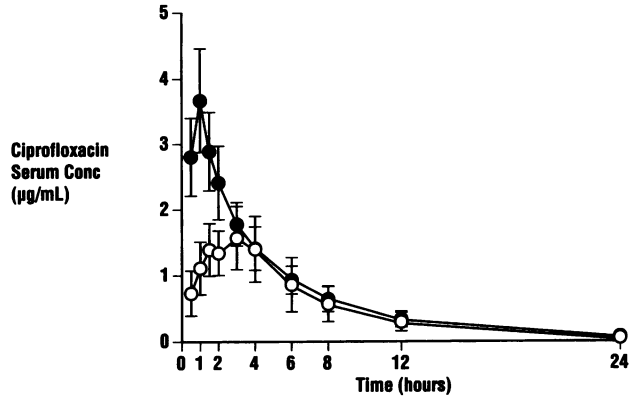

FIG. 1. Ciprofloxacin concentrations in serum versus time. Values are means ± standard deviations. ●, ciprofloxacin-water; ○, ciprofloxacin-Ensure.

DISCUSSION

Ensure administration significantly reduced the ciprofloxacin $AUC_{0-\infty}$ to 72% of the value observed when ciprofloxacin was given with water ($P = 0.00002$). One subject's $AUC_{0-\infty}$ was reduced to 52% of the water-ciprofloxacin $AUC_{0-\infty}$. The mean maximal concentration in serum when ciprofloxacin was administered with Ensure was approximately half that when it was given with water to fasted subjects. Despite a dose of 750 mg of ciprofloxacin, the mean C_{max} was only 1.99 mg/liter, which is much less than the 2.5 to 5.1 mg/liter previously reported in studies of a 750-mg single oral dose of ciprofloxacin (20, 25, 33, 34, 46). In contrast, ofloxacin absorption was significantly less affected by Ensure coadministration than ciprofloxacin ($P = 0.0016$). Although the reduction in $AUC_{0-\infty}$ with Ensure coadministration was statistically significant ($P = 0.0015$), this 12% reduction in absorption is of questionable clinical significance. The ofloxacin C_{max} achieved with the coadministration of Ensure in our study (3.48 ± 0.84 mg/liter) was similar to that reported in studies of single oral 400-mg doses given to healthy volunteers (3.2 ± 0.6 mg/liter) (7). The lowest ofloxacin-Ensure/ofloxacin-water $AUC_{0-\infty}$ ratio (74.4%) was higher than the mean ciprofloxacin-Ensure/ciprofloxacin-water AUC ratio (72%).

The absorption characteristics (C_{max}, T_{max}, $AUC_{0-\infty}$) of both fluoroquinolones when administered with water were similar to those reported by other investigators (34, 48). Ensure significantly decreased the C_{max} and $AUC_{0-\infty}$, while it lengthened the T_{max} of both drugs. The effects on bioavailability were similar to those observed with the coadministration of food (15). In our study, Ensure had the same clinically insignificant effect on ofloxacin absorption that has been reported with food (6, 26).

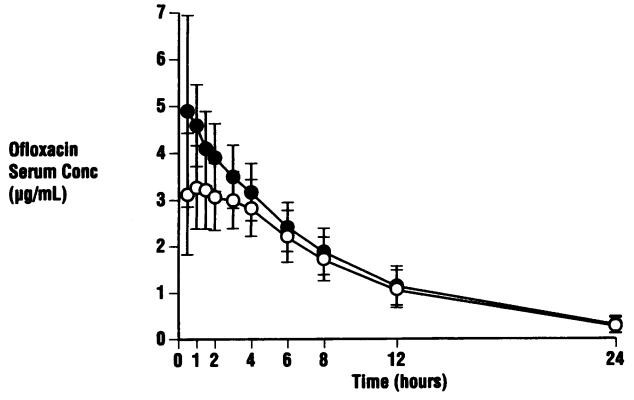

FIG. 2. Ofloxacin concentrations in serum versus time. Values are means ± standard deviations. ●, ofloxacin-water; ○, ofloxacin-Ensure.

The methodology used in the present study did not incorporate the placement of feeding tubes in the study subjects. Instead, subjects drank 120 ml of the study liquid prior to receiving the study drug and at 30-min intervals for 2 h. The pulverized study drug was mixed thoroughly in study liquid in a paper cup and ingested. Subjects rinsed the paper cup with an additional 60 ml of study liquid and immediately swallowed the remaining mixture. This procedure was used to mimic the usual preparation and administration of a dose by nursing staff for a patient receiving enteral nutrition through a feeding tube. This simulation adequately duplicates the clinical situation, because previous investigations into fluoroquinolone administration via feeding tubes have not suggested that these antibiotics bind to the tubing (5, 24, 47).

Ciprofloxacin absorption in the presence of enteral feeds has been investigated. Yuk et al. (48) reported no difference in the oral bioavailability of ciprofloxacin when it was given with water and when it was given as a crushed tablet administered with an enteral feed (Osmolite) via a nasogastric tube in six healthy volunteers. In a follow-up study (47) those same investigators administered ciprofloxacin to ICU patients receiving enteral feedings. They noted that ciprofloxacin absorption was impaired when the drug was administered via a nasogastric or gastric tube in comparison with that when it was administered via a nasoduodenal tube. However, those authors never administered ciprofloxacin with water and therefore could not assess whether a difference in ciprofloxacin absorption occurred between drug coadministered with enteral feed and water. Noer and Angaran (29) administered oral ciprofloxacin to 12 healthy volunteers with water and two enteral feeds (Osmolite and Pulmocare). Similar to our findings, they reported a significant reduction in the ciprofloxacin C_{max} ($P < 0.01$) and $AUC_{0-\infty}$ ($P < 0.0001$) when the drug was administered with both enteral products in comparison with that when it was administered with water. The ciprofloxacin-Pulmocare $AUC_{0-\infty}$ was lower than the ciprofloxacin-Osmolite $AUC_{0-\infty}$; however, no statistical analysis was reported. The difference in absorption with these two enteral feeds may be explained by the concentrations of the divalent cations calcium and magnesium. Pulmocare contains twice the concentrations of these cations as Osmolite. The enteral feed used in our study (Ensure) contains the same amount of calcium and magnesium (the two predominant divalent ions) as Osmolite. Subjects in our study received 344 mg of calcium and 138 mg of magnesium in the 660 ml of Ensure that they ingested during each of the enteral feeding study arms. No reports of enteral feeding influencing ofloxacin absorption or resulting in treatment failure have been published.

The diminution in ciprofloxacin absorption with the coadministration of Ensure observed in our study has important implications in many practice sites. Oral fluoroquinolones are particularly useful in home health care and nursing homes because of the difficulties in administering parenteral antibiotics in these settings. Additionally, clinicians practicing in hospital ICUs are being urged to switch their patients from parenteral antibiotics to less expensive oral broad-spectrum antibiotics (like fluoroquinolones) (3, 12, 13, 31, 37). Patients in home health care settings, nursing homes, and ICUs fre-

quently have sufficient comorbidities to necessitate enteral feeding. Given the results of the present study, it appears that switching from parenteral antibiotics to oral ciprofloxacin in a patient receiving Ensure could result in undesirably low concentrations in serum. Ofloxacin absorption will be significantly less affected by Ensure than ciprofloxacin absorption. Whether an interference with absorption will be noted with other enteral feeds remains to be studied. Newer fluoroquinolone antibiotics should also be investigated to determine whether their absorption profiles are also affected by enteral feed coadministration.

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REFERENCES

1. **Akerle, J. O., and A. O. Okhamafe.** 1991. Influence of oral co-administered metallic drugs on ofloxacin pharmacokinetics. J. Antimicrob. Chemother. **28**:87–94.
2. **American Society of Parenteral and Enteral Nutrition Board of Directors.** 1993. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J. Parenteral Enteral Nutr. **17**(Suppl.):20SA–21SA.
3. **Balfour, J. A., and D. Faulds.** 1993. Oral ciprofloxacin; a pharmacoeconomic evaluation of its use in the treatment of serious infections. PharmacoEconomics **3**:398–421.
4. **Cabarga, M. M., A. S. Navarro, C. I. C. Gandarillas, and A. Dominguez-Gil.** 1991. Effects of two cations on gastrointestinal absorption of ofloxacin. Antimicrob. Agents Chemother. **35**:2102–2105.
5. **Druckenbrod, R. W., and D. P. Healy.** 1992. In vitro delivery of crushed ciprofloxacin through a feeding tube. Ann. Pharmacother. **26**:494–495.
6. **Dudley, M. N., C. R. Marchbanks, S. C. Flor, and B. Beals.** 1991. The effect of food or milk on the absorption kinetics of ofloxacin. Eur. J. Clin. Pharmacol. **41**:569–571.
7. **Flor, S.** 1989. Pharmacokinetics of ofloxacin. Am. J. Med. **87**(Suppl. 6C):24S–30S.
8. **Flor, S., D. R. P. Guay, J. A. Opsahl, K. Tack, and G. R. Matzke.** 1990. Effects of magnesium-aluminum hydroxide and calcium carbonate antacids on bioavailability of ofloxacin. Antimicrob. Agents Chemother. **34**:2436–2438.
9. **Frost, R. W., J. D. Carlson, A. J. Dietz, A. Heyd, and J. T. Lettieri.** 1989. Ciprofloxacin pharmacokinetics after a standard or high-fat/high calcium breakfast. J. Clin. Pharmacol. **29**:953–955.
10. **Garrelts, J. C., P. J. Godley, J. D. Peterie, E. H. Gerlach, and C. C. Yakshe.** 1990. Sucralfate significantly reduces ciprofloxacin concentrations in serum. Antimicrob. Agents Chemother. **34**:9341–9343.
11. **Granneman, G. R., and L. L. Varga.** 1991. High-performance liquid chromatographic procedures for the determination of temafloxacin in biological matrices. J. Chromatogr. **413**:199–206.
12. **Grasela, T. H., J. A. Paladino, J. J. Schentag, D. Huepenbecker, J. Rybacki, J. B. Purcell, and J. B. Fiedler.** 1991. Clinical and economic impact of oral ciprofloxacin as a follow-up to parenteral antibiotics. DICP Ann. Pharmacother. **25**:857–862.
13. **Guay, D. R. P.** 1993. Sequential antimicrobial therapy: a realistic approach to cost containment. PharmacoEconomics **3**:341–344.
14. **Höffken, G., K. Borner, T. D. Glatzel, P. Koeppe, and H. Lode.** 1985. Reduced enteral absorption of ciprofloxacin in the presence of antacids. Eur. J. Clin. Microbiol. **4**:345–348.
15. **Höffken, G., H. Lode, R. Wiley, T. D. Glatzel, D. Sievers, T. Olschewski, K. Borner, and T. Koeppe.** 1988. Pharmacokinetics and bioavailability of ciprofloxacin and ofloxacin: effect of food and acid intake. Rev. Infect. Dis. **10**(Suppl. 1):S138–S139.
16. **Hooper, W. D., R. G. Dickinson, and M. J. Eadie.** 1990. Effect of food on absorption of lomefloxacin. Antimicrob. Agents Chemother. **34**:1797–1799.
17. **Kara, M., B. B. Hasinoff, D. W. McKay, and R. C. Campbell.** 1991. Clinical and chemical interactions between iron preparations and ciprofloxacin. Br. J. Clin. Pharmacol. **31**:257–261.
18. **Kivistö, K. T., P. Ojala-Karlsson, and P. J. Neuvonen.** 1992. Inhibition of norfloxacin absorption by dairy products. Antimicrob. Agents Chemother. **36**:489–491.
19. **Leroy, A., F. Forsa, G. Humbert, P. Bernadet, and J. P. Fillastre.** 1987. The pharmacokinetics of ofloxacin in healthy adult male volunteers. Eur. J. Clin. Pharmacol. **31**:629–630. (Letter.)
20. **Lettieri, J. T., M. C. Rogge, L. Kaiser, R. M. Echols, and A. H. Heller.** 1992. Pharmacokinetic profiles of ciprofloxacin after single intravenous and oral doses. Antimicrob. Agents Chemother. **36**:993–996.
21. **Lomaestro, B. M., and G. R. Bailie.** 1991. Effect of staggered dose of calcium on the bioavailability of ciprofloxacin. Antimicrob. Agents Chemother. **35**:1004–1007.
22. **Lomaestro, B. M., and G. R. Bailie.** 1991. Quinolone-cation interactions: a review. DICP Ann. Pharmacother. **25**:1249–1258.
23. **Lomaestro, B. M., and T. S. Lesar.** 1989. Concurrent administration of ciprofloxacin and potentially interacting drugs. Am. J. Hosp. Pharm. **46**:1770. (Letter.)
24. **Lubowski, T. J., C. H. Nightingale, K. Sweeny, and R. Quintiliani.** 1992. The relative bioavailability of temafloxacin administered through a nasogastric tube with and without enteral feeding. Clin. Pharmacokinet. **22**(Suppl. 1):43–47.
25. **McEvoy, G. K. (ed.).** 1993. Quinolones, p. 440–472. *In* American hospital formulary service drug information 1993. American Society of Hospital Pharmacists, Bethesda, Md.
26. **Neuvonen, P. J., and K. T. Kivistö.** 1992. Milk and yoghurt do not impair the absorption of ofloxacin. Br. J. Clin. Pharmacol. **33**:346–348.
27. **Neuvonen, P. J., K. T. Kivistö, and P. Lehto.** 1991. Interference of dairy products with the absorption of ciprofloxacin. Clin. Pharmacol. Ther. **50**:498–502.
28. **Nix, D. E., W. A. Watson, M. E. Lener, R. W. Frost, G. Krol, H. Goldstein, J. Lettieri, and J. J. Schentag.** 1989. Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. Clin. Pharmacol. Ther. **46**:700–705.
29. **Noer, B. L., and D. M. Angaran.** 1990. The effect of enteral feedings on ciprofloxacin pharmacokinetics. Pharmacotherapy **10**:254. (Abstract.)
30. **Noyes, M., and R. E. Polk.** 1988. Norfloxacin and absorption of magnesium-aluminum. Ann. Intern. Med. **109**:168–169. (Letter.)
31. **Paladino, J. A., H. E. Sperry, J. M. Backes, J. A. Gelber, D. J. Serrianne, T. J. Cumbo, and J. J. Schentag.** 1991. Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. Am. J. Med. **91**:462–470.
32. **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.
33. **Physicians' Desk Reference.** 1993. Physician's drug reference, 47th ed., p. 1633–1636. Medical Economics Data, Montvale, N.J.
34. **Plaisance, K. I., G. L. Drusano, A. Forrest, C. I. Bustamante, and H. C. Standiford.** 1987. Effect of dose size on bioavailability of ciprofloxacin. Antimicrob. Agents Chemother. **31**:956–958.
35. **Polk, R. E.** 1989. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am. J. Med. **87**(Suppl. 5A):76S–81S.
36. **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.
37. **Powers, T., and D. H. Bingham.** 1990. Clinical and economic effect of ciprofloxacin as an alternative to injectable antimicrobial therapy. Am. J. Hosp. Pharm. **47**:1781–1784.
38. **Preheim, L. C., T. A. Cuevas, J. S. Roccaforte, M. A. Mellencamp, and M. J. Bittner.** 1986. Ciprofloxacin and antacids. Lancet **ii**:48. (Letter.)
39. **Sahai, J., K. Gallicano, L. Oliveras, S. Khaliq, N. Hawley-Foss, and G. Farber.** 1993. Cations in the didanosine tablet reduce ciprofloxacin bioavailability. Clin. Pharmacol. Ther. **53**:292–297.
40. **Sahai, J., D. P. Healy, J. Stotka, and R. E. Polk.** 1993. The

influence of chronic administration of calcium carbonate on the bioavailability of oral ciprofloxacin. Br. J. Clin. Pharmacol. **35:** 302–304.

41. **Shimada, J., K. Shiba, T. Oguma, H. Miwa, Y. Yoshimura, T. Nishikawa, Y. Okabayashi, T. Kitagawa, and S. Yamamoto.** 1992. Effect of antacid on absorption of the quinolone lomefloxacin. Antimicrob. Agents Chemother. **36:**1219–1224.
42. **Somogyi, A. A., F. Bochner, J. A. Keal, P. E. Rolan, and M. Smith.** 1987. Effect of food on enoxacin absorption. Antimicrob. Agents Chemother. **31:**638–639.
43. **Sörgel, F., G. Mahr, U. Stephan, H. U. Koch, and H. G. Wiesemann.** 1988. Effect of normal and fat-rich food on the absorption of pefloxacin in humans. Rev. Infect. Dis. **10**(Suppl. 1)**:**S137–S138.
44. **Van Slooten, A. D., D. E. Nix, J. H. Wilton, J. H. Love, J. M. Spivey, and H. R. Goldstein.** 1991. Combined use of ciprofloxacin and sucralfate. DICP Ann. Pharmacother. **25:**578–582.
45. **Verho, M., V. Malerczyk, E. Dagrosa, and A. Korn.** 1986. The effect of food on the pharmacokinetics of ofloxacin. Curr. Med. Res. Opin. **10:**166–171.
46. **Weinstein, M. P., R. G. Deeter, K. A. Swanson, and J. S. Gross.** 1991. Crossover assessment of serum bactericidal activity and pharmacokinetics of ciprofloxacin alone and in combination in healthy elderly volunteers. Antimicrob. Agents Chemother. **35:** 2352–2358.
47. **Yuk, J. H., C. H. Nightingale, R. Quintiliani, N. S. Yeston, R. Orlando, E. D. Dobkin, J. C. Kambe, K. R. Sweeney, and E. A. Buonpane.** 1990. Absorption of ciprofloxacin administered through a nasogastric or a nasoduodenal tube in volunteers and patients receiving enteral nutrition. Diagn. Microbiol. Infect. Dis. **13:**99–102.
48. **Yuk, J. H., C. H. Nightingale, K. R. Sweeny, R. Quintiliani, J. T. Lettieri, and R. W. Frost.** 1989. Relative bioavailability in healthy volunteers of ciprofloxacin administered through a nasogastric tube with and without enteral feeding. Antimicrob. Agents Chemother. **33:**1118–1120.
49. **Yuk, J. H., and T. W. Williams.** 1991. Drug interaction with quinolone antibiotics in intensive care unit patients. Arch. Intern. Med. **151:**619. (Letter.)