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Influence of Intravenously Administered Ciprofloxacin on Aerobic Intestinal Microflora and Fecal Drug Levels When Administered Simultaneously with Sucralfate

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Ciprofloxacin, when given intravenously (i.v.), is secreted in significant amounts via the mucosa into the intestinal lumen. Sucralfate inhibits the antimicrobial activity of ciprofloxacin. The effect of combined therapy on the intestinal flora was investigated in 16 healthy volunteers. They were randomly assigned to two groups. Group A received 2 g of sucralfate orally three times a day for 7 days and 400 mg of ciprofloxacin i.v. twice a day (b.i.d.) starting 3 days after the sucralfate administration began. Group B was given only 400 mg of ciprofloxacin i.v. b.i.d. for 4 days. A total of 9 stool samples were collected from each subject beginning the week before ciprofloxacin was administered and on days −1, 1, 2, 3, 4, 7, 9, and 10 or 11 after commencement of the infusion period. The aerobic fecal flora was determined by standard microbiological methods. Measurements of fecal ciprofloxacin levels were based on high-performance liquid chromatography. Counts of bacteria of the family *Enterobacteriaceae* decreased in all subjects and were below 10^2 CFU/g in eight of eight subjects (group A) and six of eight subjects (group B) on day 4, but they returned to normal in all but one subject (group A) 10 days after the last infusion. The decreases in levels of bacteria of the family *Enterobacteriaceae* were not significantly different in groups A and B (Kaplan-Meier test). Staphylococci and nonfermenters responded variably, enterococci and lactobacilli remained unchanged, and candida levels increased transiently in four subjects (two in each group). Maximum fecal drug levels ranged from 251 to 811 μg/g. No significant difference could be found between the two groups. The i.v. application of ciprofloxacin eliminates intestinal bacteria of the family *Enterobacteriaceae* in a rapid and selective manner. This effect is not affected by simultaneous oral application of sucralfate.

Ciprofloxacin is a highly active fluoroquinolone antibacterial agent with a broad spectrum of activity, especially against aerobic gram-negative rod bacteria. Ciprofloxacin is secreted by the intestinal mucosa, even when given intravenously (6, 25, 31), and thus may affect the intestinal flora (29).

Sucralfate is the aluminum salt of saccharose octasulfate, which has a protective effect on gastrointestinal mucosa by various mechanisms (10, 13, 33). It may inhibit the antimicrobial activity of fluoroquinolones by chelate binding (11, 20, 21), so that maximum levels of orally applied ciprofloxacin in serum are reached with delay and amount to only 10% of the usual values (3, 11, 38).

This study was performed to demonstrate the influence of intravenously administered ciprofloxacin on the intestinal microflora and to find out whether this effect is altered when sucralfate is given simultaneously.

MATERIALS AND METHODS

Subjects and design. Sixteen volunteers participated in the study after informed consent was obtained. The study was open, randomized, and prospectively conducted. All volunteers were found to be healthy by clinical examination and laboratory tests. Drugs other than the study drugs were not taken by any of the participants for 4 weeks before and during the study period. They all maintained a normal Western-type diet throughout the study. The volunteers were randomly allocated to group A (sucralfate for 7 days and ciprofloxacin for 4 days) or group B (ciprofloxacin only for 4 days). Group A consisted of 1 female and 7 male volunteers, aged 20 to 30 years (mean, 28), with body weights of 52.0 to 81.0 kg (mean, 73.5). Group B comprised 3 female and 5 male volunteers, aged 20 to 36 years (mean, 26.5), with body weights of 54.0 to 75.0 kg (mean, 70.0). The study protocol was approved by the Ethics Committee of the Faculty of Medicine of the Ludwig-Maximilians-Universität Munich.

Drug administration and dosages. All volunteers received 400 mg of ciprofloxacin (Bayer AG, Leverkusen, Germany) as an intravenous (i.v.) infusion over 60 min every 12 h for 4 days before they had their meals. The volunteers of group A took 10 ml (i.e., 2 g) of an oral sucralfate suspension (Merck, Darmstadt, Germany) every 8 h during the course of these 4 days, as well as 3 days before the start of ciprofloxacin administration.

The i.v. infusions were given in a ward of our hospital, and the volunteers were monitored by a physician for at least 1 h after the end of the infusions.

Feces sampling and sampling schedule. Aliquots of 30 to 50 g of feces were collected in sterile plastic tubes, homogenized, and kept at 4°C. Parts of the specimens were stored at −80°C for determination of ciprofloxacin levels. Feces were sampled once during the week before the study, once the day before the first administration of ciprofloxacin, every day during the application period, and 1, 3, 5, and 10 or 11 days after the end of the administration period.

Identification and counting of fecal microorganisms. All samples were processed microbiologically within 24 h of sampling. A weighed portion of feces was suspended 1:10 in stool buffer (4.5 g of KH_2PO_4, 6.0 g of Na_2HPO_4, 0.5 g of cysteine-hydrochloride, and 1.0 g of Tween 80 in 1,000 ml of distilled water) and further diluted with 0.9% NaCl up to $1:10^9$. One hundred microliters of appropriate dilutions were then plated onto the following media: Columbia agar base with 5% sheep blood (Becton Dickinson, Heidelberg, Germany), Endo agar (Oxoid, Wesel, Germany), MacConkey agar (Oxoid), mannitol salt agar (Oxoid), Slanetz-Bartley agar (Oxoid), Rogosa agar (Merck), Sabouraud agar (our own preparation), and Mueller-Hinton agar II with 2 mg of ciprofloxacin per liter (Oxoid). The detection threshold was 10^2 CFU/g. The media were incubated at 37°C for at least 48 h under aerobic conditions. Blood agar plates were cultured in an atmosphere of 5% CO_2. Colonies were counted and identified by selective properties of the media used and the usual microscopic and biochemical methods (Gram's stain, Api 20 E, Api 20 NE; BioMérieux, Nürtingen, Germany).

Determination of ciprofloxacin levels in feces by HPLC. The sample preparation and measurement of ciprofloxacin by high-performance liquid chromatography (HPLC) and fluorescence detection was performed exactly as described by Scholl et al. (30). This method has been validated according to quality assurance measurements and issues of linearity of recovery. Ciprofloxacin and its four known metabolites may be differentiated exactly, and the recovery of ciprofloxacin in feces was 89.5% (30). In our assay, the limit of quantification was 0.15 μg/g and the response from calibration standards was linear from 0.15 to 20.0 μg/g.

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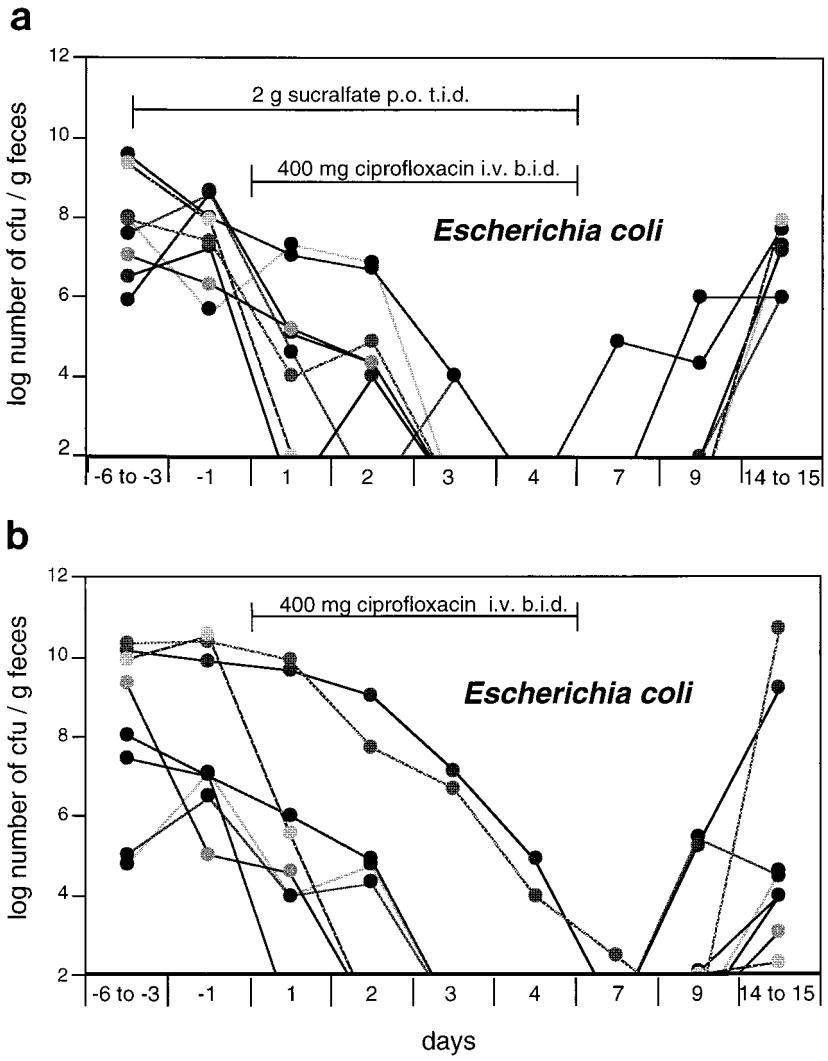

FIG. 1. (a) Fecal colony counts of *E. coli* in eight healthy volunteers receiving 400 mg of ciprofloxacin i.v. twice a day (b.i.d.) for 4 days and 2 g of sucralfate orally (p.o.) three times a day (t.i.d.) for 7 days. (b) Fecal colony counts of *E. coli* in eight healthy volunteers receiving 400 mg of ciprofloxacin i.v. b.i.d. for 4 days.

Precision control standards for 10.0 μg/g yielded 10.31 μg/g ± 6.1%; for 0.625 μg/g, the yield was 0.629 μg/g ± 7.2%. Recovery of ciprofloxacin at a concentration of 12.5 μg/g was 86.1% ± 16.0% and 84.7% ± 10.2% after pretreatment with sucralfate for 3 days.

Statistical analysis. The decrease in counts of bacteria of the family *Enterobacteriaceae* was plotted as a Kaplan-Meier curve. A log rank test was applied to detect differences between the two groups. Wilcoxon's test for unmatched pairs was applied to compare fecal drug levels. For comparison of fecal levels of ciprofloxacin related to colony counts of *Escherichia coli*, the arithmetic mean of $\log(x + 1)$ was set for ciprofloxacin at <200 μg/g, 200 to 400 μg/g, 400 to 600 μg/g and >600 μg/g. Colony counts below the detection threshold were assumed to be 0 for this calculation.

RESULTS

Intestinal flora. Before the administration of ciprofloxacin, *E. coli* was the predominant species of the family *Enterobacteriaceae* in all subjects but one, in whom *Citrobacter diversus* was predominant. In group A, *E. coli* levels decreased to $<10^2$ CFU/g in all eight subjects after 4 days; in group B, they persisted at 10^4 and 10^5 CFU/g in two subjects but were below the detection threshold in all subjects at 3 and 5 days after the last infusion, respectively (Fig. 1). Bacteria of the family *Enterobacteriaceae* other than *E. coli* were found in seven of eight subjects in each group. Their levels fell below 10^2 CFU/g in all subjects after 4 days of i.v. administration of ciprofloxacin (Fig. 2). By 10 to 11 days after the infusion period, the coliform flora had returned to normal in all but one subject (group A). There was no significant difference in the decrease of the levels of bacteria of the family *Enterobacteriaceae* between the two groups (log rank, 0.22; $P = 0.64$).

Nonfermenters were detected in five subjects of group A and in seven subjects of group B, mostly during and after the infusions (Fig. 2); the detected strains were resistant to ciprofloxacin in four cases (three *Pseudomonas* spp. and one *Acinetobacter* sp.).

Staphylococcus aureus was initially present in low counts in two subjects of group A and three subjects of group B and subsequently disappeared totally after 2 days of ciprofloxacin administration.

Coagulase-negative staphylococci were found in seven subjects of each group at levels ranging from 10^2 to 10^6 CFU/g, and they responded variably, disappearing in some cases and persisting in others. Resistant coagulase-negative staphylococci were found in only one subject before ciprofloxacin was

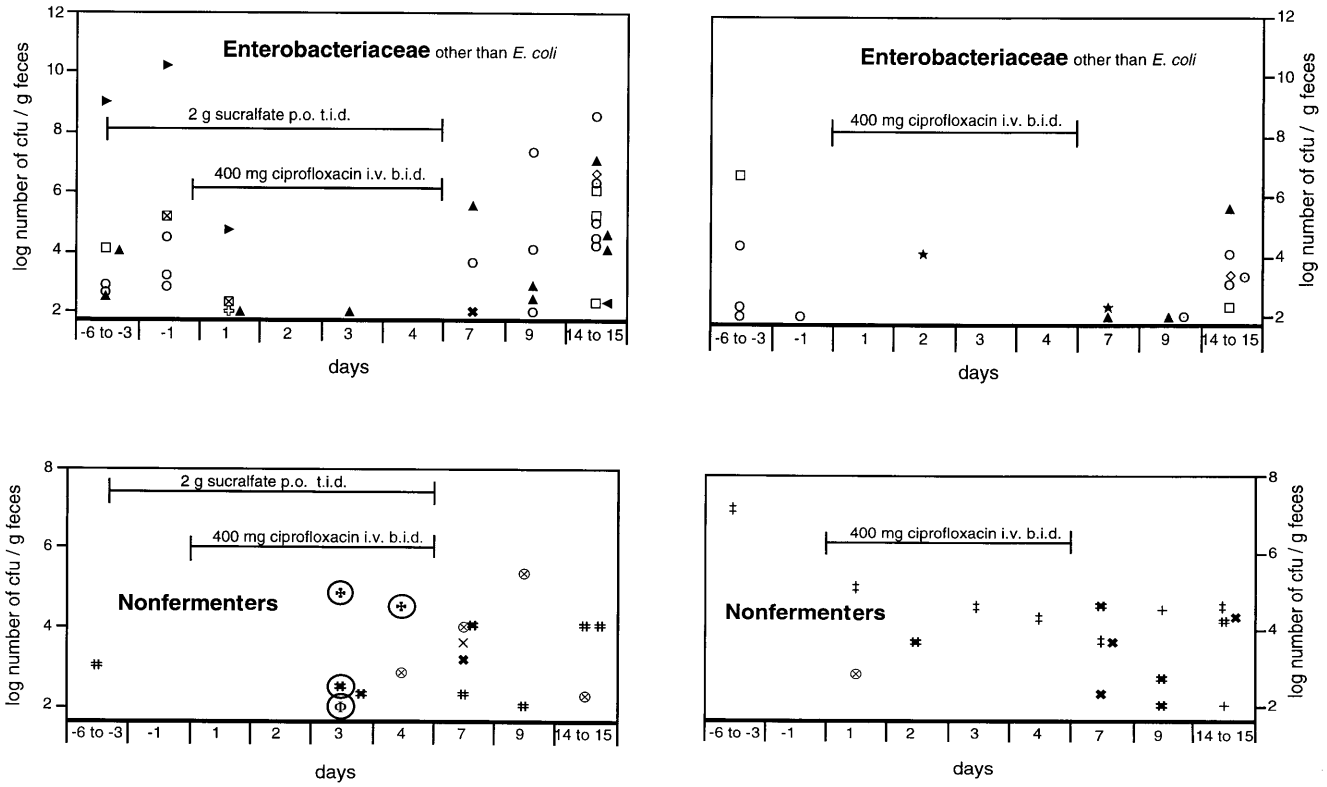

FIG. 2. Fecal colony counts in 16 healthy volunteers receiving 400 mg of ciprofloxacin i.v. twice a day (b.i.d.) for 4 days. Eight volunteers had 2 g of sucralfate orally (p.o.) three times a day (t.i.d.) for 7 days. *Enterobacteriacea* other than *E. coli*: ◀, *Citrobacter amalonaticus*; ▶, *Citrobacter diversus*; ▲, *Citrobacter freundii*; ⊠, *Enterobacter aerogenes*; □, *Enterobacter cloacae*; ◇, *Hafnia alvei*; ○, *Klebsiella pneumoniae*; ⊙, *Klebsiella oxytoca*; ★, *Morganella morganii*; △, *Providencia rettgeri*; ✣, *Salmonella enteritidis*; ×, *Yersinia enterocolitica*. Nonfermenters: Φ, *Acinetobacter* sp.; ⊗, *Alcaligenes xylosoxidans*; ×, *Comamonas acidovorans*; ⋕, *Pseudomonas aeruginosa*; ‡, *Pseudomonas alcaligenes*; +, *Pseudomonas putida*; ⋇, *Pseudomonas vesicularis*; ⋕, *Pseudomonas* sp.; ✖, *Stenotrophomonas maltophilia.*

given (group A). Their levels increased from 10^2 to 10^6 CFU/g during the course of ciprofloxacin administration and returned to 10^3 CFU/g 10 days after the end of the administration period. Ciprofloxacin-resistant coagulase-negative staphylococci were found in 5 of 16 volunteers after the infusion period. The increase in number of volunteers colonized by resistant staphylococci was not significant by Fisher's exact test (P was 0.086 for the one-sided test).

Enterococci were present at 10^4 to 10^{10} CFU/g in all volunteers, and their levels were reduced to less than 1/100 of the baseline values in two subjects in each group. In all other subjects, the counts of enterococci remained stable. There was no increase in the levels of enterococci resistant to ciprofloxacin. Lactobacilli were found in all subjects at 10^4 to 10^{10} CFU/g and remained at a constant level.

Candida were present at levels of 10^2 to 10^5 CFU/g in all volunteers. Their levels increased by more than 100-fold in two subjects of each group and dropped again in two of these while ciprofloxacin was still being given.

Fecal levels of ciprofloxacin. Peak fecal levels of ciprofloxacin were found on the 3rd and 4th days of the administration of ciprofloxacin and ranged from 251 to 811 μg/g (group A) and 315 to 714 μg/g (group B) (Fig. 3). Wilcoxon's test for unmatched pairs did not show a significant difference in fecal levels between the two groups.

E. coli could still be found when fecal levels of ciprofloxacin reached 385 μg/g (group A) and 578 μg/g (group B). There was no evidence that ciprofloxacin was less effective in reducing *E. coli* in group A (Fig. 4).

Side effects. Ciprofloxacin was well tolerated by all volunteers, and only minor side effects were seen (two cases of flatulence, two cases of fatigue, and two reports by one subject of mild vertigo after i.v. infusion).

DISCUSSION

The effect of orally administered ciprofloxacin on the fecal flora has been shown in several studies (1, 4, 9, 14, 22, 26). The studies involved healthy volunteers and patients. Ciprofloxacin was administered at doses between 500 and 1,000 mg daily, ranging from a single dose (22) to a duration of 42 days (26). All studies showed a marked decrease in levels of coliform bacteria. These organisms were under the detection threshold in all subjects after 3 to 5 days (14, 26) or after 7 days, depending on the sampling schedule of these studies (4). This corresponds well to the results shown here, as we found a suppression of bacteria of the family *Enterobacteriaceae* after 2 to 4 days, but with the important difference that ciprofloxacin was given intravenously in this investigation.

The effect of intravenous ciprofloxacin on other constituents of the intestinal flora also corresponds to the results obtained after oral administration in other studies. Staphylococcal levels had either not been affected (1, 9, 22) or decreased after oral administration of ciprofloxacin (4). We saw a decrease in *S. aureus* levels, which does not regularly occur in the intestinal flora. On the other hand, we found an increase in the occurrence of ciprofloxacin-resistant coagulase-negative staphylococci. This increase, however, was not statistically significant.

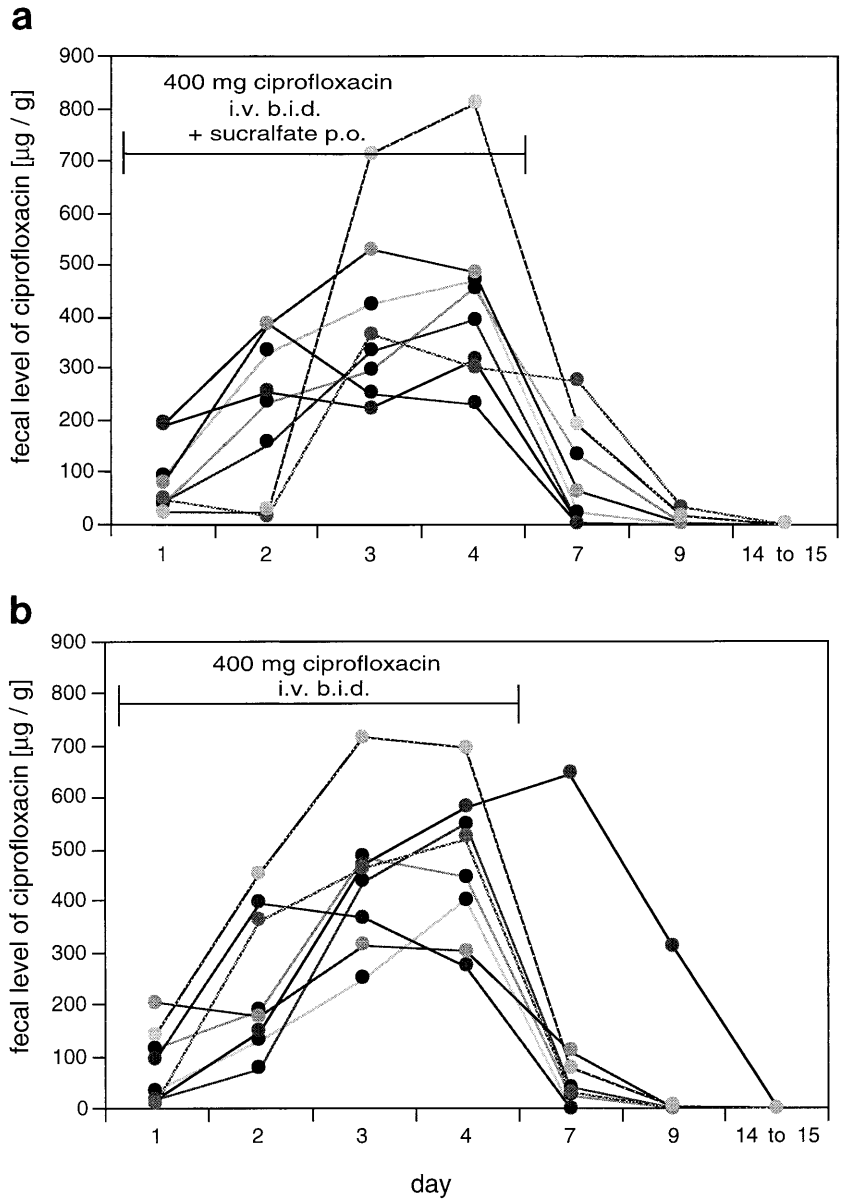

FIG. 3. (a) Fecal levels of ciprofloxacin in eight healthy volunteers receiving 400 mg of ciprofloxacin i.v. twice a day (b.i.d.) for 4 days and 2 g of sucralfate orally (p.o.) three times a day (t.i.d.) for 7 days, as measured by HPLC. (b) Fecal levels of ciprofloxacin in eight healthy volunteers receiving 400 mg of ciprofloxacin i.v. b.i.d. for 4 days, as measured by HPLC.

Counts of enterococci remained stable (22) or decreased after oral ciprofloxacin (1, 4, 26). Here too, we observed both effects in our volunteers after intravenous administration of ciprofloxacin. An increase in candida levels has been described by other investigators (4, 35), and candida levels also increased in 4 of the 16 volunteers participating in our study. In two of those, however, candida levels decreased while ciprofloxacin was still being given, suggesting that other causes might also have influenced the candida population in the gut.

Approximately 75% of an oral dose of ciprofloxacin is excreted in urine, and 25% is found in feces (7, 17). Ciprofloxacin levels in feces may vary but considerably exceed the corresponding levels in serum. After a 7-day oral course of 500 mg of ciprofloxacin twice a day, ciprofloxacin fecal levels of 185 to 2,220 μg/g were found in healthy volunteers (4). This is only partly due to incomplete absorption, since approximately 15% of a dose is found in feces after intravenous application (25). Whereas the amount of biliary excretion is very low, transintestinal secretion is a pharmacokinetic property of ciprofloxacin (6, 31, 37). This way of elimination can amount to up to 50% of the total body clearance in cases of renal insufficiency (25). Studies in animals have shown that most of the transintestinal secretion occurs in the small intestine (23, 27, 28). Even though the carrier system for quinolones needs to be defined (15), the transepithelial transport of ciprofloxacin is an active and saturable process (12). This may explain why the levels of ciprofloxacin in feces after intravenous application in our study were in the same range as those reported after oral application (251 to 811 μg/g and 185 to 2,220 μg/g, respectively) (4). It furthermore explains why the changes in intestinal microflora are very similar after oral and intravenous administration of ciprofloxacin, as discussed above.

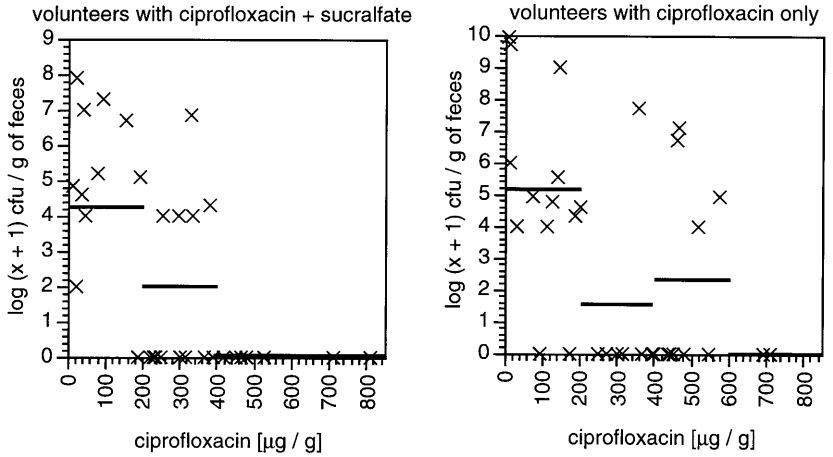

FIG. 4. Fecal levels of ciprofloxacin with corresponding log(x + 1) of *E. coli* in 16 healthy volunteers receiving 400 mg of ciprofloxacin i.v. twice a day for 4 days. Eight volunteers had 2 g of sucralfate orally three times a day for 7 days. Horizontal bars signify arithmetic means of log(x + 1) for ciprofloxacin at <200 μg/g, 200 to 400 μg/g, 400 to 600 μg/g, and >600 μg/g.

When HPLC is used for the measurement of drug levels, there is no evidence as to how much of the drug is still antimicrobially active. For norfloxacin, the paradox of high levels in feces and a moderate effect on fecal aerobic gram-positive and anaerobic microflora has been investigated. The reason for this effect is a reversible binding of norfloxacin to feces, which has been confirmed for ciprofloxacin as well by competitive binding studies with ^{14}C-labeled norfloxacin (8). As is also the case for nonfermenters, the MICs of quinolone antibiotics are more than 100 times higher in the presence of fecal material (36). This explains why we found nonfermenters which were not resistant to ciprofloxacin while the drug levels were markedly above the usual MICs. The same applies to enterococci, which are moderately susceptible to ciprofloxacin but whose levels were usually not reduced even though this could have been expected with regard to the high levels of ciprofloxacin. Finally, this effect was true for bacteria of the family *Enterobacteriaceae* as well. Whereas no resistant strains of *E. coli* were detected on plates with 2 mg of ciprofloxacin per liter, these organisms still grew when ciprofloxacin levels reached up to 578 μg/g of feces (Fig. 4).

There are four known metabolites of ciprofloxacin (desethylene-, sulfo-, oxo-, and formylciprofloxacin). As none of them is as microbiologically active as ciprofloxacin, it may well be assumed that the antimicrobial effect we observed is mostly due to ciprofloxacin itself (34, 39). Sucralfate itself may have a bacteriostatic effect on bacteria of the family *Enterobacteriaceae* under certain conditions (2, 5, 16). In the setting of our study this effect was not relevant, as there was virtually no change in fecal flora after a 3-day pretreatment with sucralfate in group A.

The simultaneous oral application of ciprofloxacin and sucralfate leads to insoluble complexes, with the result that antimicrobial activity is inhibited and only 10% of the ciprofloxacin is absorbed (3, 11, 38). Even when ciprofloxacin is administered 6 h after sucralfate, there is a remarkable decrease in ciprofloxacin bioavailability, ranging between 30 and 50% (20). In comparison with this, there is a rather modest interaction between sucralfate and other quinolones, such as norfloxacin, ofloxacin, or fleroxacin (18, 19). Neither with respect to the influence on the aerobic microflora nor with respect to the levels of ciprofloxacin did we find any difference when sucralfate was given concomitantly. Furthermore, there was no evidence for a decrease in antimicrobial activity in the presence of sucralfate when the effects of fecal ciprofloxacin levels on colony counts of *E. coli* were compared (Fig. 4). This is in contrast to the binding of transintestinally secreted ciprofloxacin by orally administered charcoal, a model that was used for pharmacokinetic studies by Sörgel and coworkers (31). The interaction of sucralfate and ciprofloxacin is based on chelate binding between aluminum ions of sucralfate and the 4-oxo and 3-carboxy groups of fluoroquinolones (20). Aluminum dissociates from sucralfate mainly at low pH in the stomach (24). This might contribute to the profound drug interaction, as orally applied ciprofloxacin is mainly absorbed in the upper gastrointestinal tract (32). As secretion of ciprofloxacin mainly takes place in the ileum (23), we can only speculate that fewer aluminum ions must have been available for the binding of ciprofloxacin in this part of the gastrointestinal tract.

The results obtained in our study involving healthy volunteers show a rapid suppression of bacteria of the family *Enterobacteriaceae* in the gut after intravenously administered ciprofloxacin irrespective of a simultaneous administration of sucralfate.

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REFERENCES

1. **Bergan, T., C. Delin, S. Johansen, I. M. Kolstad, C. E. Nord, and S. B. Thorsteinsson.** 1986. Pharmacokinetics of ciprofloxacin and effect of repeated dosage on salivary and fecal microflora. Antimicrob. Agents Chemother. **29:**298–302.
2. **Bergmans, D., M. Bonten, C. Gaillard, F. van Thiel, S. van der Geest, and E. Stobberingh.** 1994. In vitro antibacterial activity of sucralfate. Eur. J. Clin. Microbiol. Infect. Dis. **13:**615–620.
3. **Brouwers, J. R. B., H. J. v. d. Kam, J. Sijtsma, and C. H. W. Koks.** 1989. Important drug interaction of oral ciprofloxacin with sucralfate and magnesium citrate solution. Pharm. Weekbl. **11:**13.
4. **Brumfitt, W., I. Franklin, D. Grady, J. M. T. Hamilton-Miller, and A. Iliffe.** 1984. Changes in the pharmacokinetics of ciprofloxacin and fecal flora during administration of a 7-day course to human volunteers. Antimicrob. Agents Chemother. **26:**757–761.

5. **Daschner, F., I. Kappstein, and I. Engels.** 1987. Antibakterielle Aktivität von Sucralfat in künstlichem Magensaft. Intensivmedizin. **24:**163–166.
6. **Dörner, A., A. Witthohn, and E. Kraas.** 1990. Ciprofloxacin prior to colon surgery. Diagn. Microbiol. Infect. Dis. **13:**177–179.
7. **Drusano, G. L.** 1987. An overview of the pharmacology of intravenously administered ciprofloxacin. Am. J. Med. **82:**339–345.
8. **Edlund, C., L. Lindqvist, and C. E. Nord.** 1988. Norfloxacin binds to human fecal material. Antimicrob. Agents Chemother. **32:**1869–1874.
9. **Esposito, S., D. Barba, G. B. Galante, and O. Laghezza.** 1988. Changes in intestinal microflora and treatment of portal systemic encephalopathy. Rev. Infect. Dis. **10:**197.
10. **Folkman, J., S. Szabo, M. Stovroff, P. Mcneil, W. Li, and Y. Shing.** 1991. Duodenal ulcer. Discovery of a new mechanism and development of angiogenic therapy that accelerates healing. Ann. Surg. **214:**414–427.
11. **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:**931–933.
12. **Griffiths, N. M., B. H. Hirst, and N. L. Simmons.** 1994. Active intestinal secretion of the fluoroquinolone antibacterials ciprofloxacin, norfloxacin and pefloxacin; a common secretory pathway? J. Pharmacol. Exp. Ther. **269:**496–502.
13. **Hollander, D., and A. Tarnawski.** 1990. The protective and therapeutic mechanisms of sucralfate. Scand. J. Gastroenterol. **25:**1–5.
14. **Holt, H. A., D. A. Lewis, L. O. White, S. Y. Bastable, and D. S. Reeves.** 1986. Effect of oral ciprofloxacin on the fecal flora of healthy volunteers. Eur. J. Clin. Microbiol. Infect. Dis. **5:**201–205.
15. **Jaehde, U., F. Sörgel, A. Reiter, G. Sigl, K. G. Naber, and W. Schunack.** 1995. Effect of probenecid on the distribution and elimination of ciprofloxacin in humans. Clin. Pharmacol. Ther. **58:**532–541.
16. **Kappstein, I., and I. Engels.** 1987. Antibacterial activity of sucralfate and bismuth subsalicylate in simulated gastric fluid. Eur. J. Clin. Microbiol. Infect. Dis. **6:**216–217.
17. **LeBel, M.** 1988. Ciprofloxacin: chemistry, mechanism of action, resistance, antimicrobial spectrum, pharmacokinetics, clinical trials, and adverse reactions. Pharmacotherapy **8:**3–33.
18. **Lehto, P., and K. T. Kivistö.** 1994. Effect of sucralfate on absorption of norfloxacin and ofloxacin. Antimicrob. Agents Chemother. **38:**248–251.
19. **Lubowski, T. J., C. H. Nightingale, K. Sweeney, and R. Quintiliani.** 1992. Effect of sucralfate on pharmacokinetics of fleroxacin in healthy volunteers. Antimicrob. Agents Chemother. **36:**2758–2760.
20. **Nix, D. E., W. A. Watson, L. Handy, R. W. Frost, D. L. Rescott, and H. R. Goldstein.** 1989. The effect of sucralfate pretreatment on the pharmacokinetics of ciprofloxacin. Pharmacotherapy **9:**377–380.
21. **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.
22. **Pecquet, S., S. Ravoire, and A. Andremont.** 1990. Faecal excretion of ciprofloxacin after a single oral dose and its effect on faecal bacteria in healthy volunteers. J. Antimicrob. Chemother. **26:**125–129.
23. **Ramon, J., S. Dautrey, R. Farinoti, C. Carbon, and E. Rubinstein.** 1994. Intestinal elimination of ciprofloxacin in rabbits. Antimicrob. Agents Chemother. **38:**757–760.
24. **Robertson, J. A., I. B. Salusky, W. G. Goodman, K. C. Norris, and J. W. Coburn.** 1989. Sucralfate, intestinal aluminum absorption, and aluminium toxicity in a patient on dialysis. Ann. Intern. Med. **111:**179–181.
25. **Rohwedder, R. W., T. Bergan, S. B. Thorsteinsson, and H. Scholl.** 1990. Transintestinal elimination of ciprofloxacin. Diagn. Microbiol. Infect. Dis. **13:**127–133.
26. **Rozenberg-Arska, M., A. W. Dekker, and J. Verhoef.** 1985. Ciprofloxacin for selective decontamination of the alimentary tract in patients with acute leukemia during remission induction treatment: the effect on fecal flora. J. Infect. Dis. **152:**104–107.
27. **Rubinstein, E., S. Dautrey, R. Farinoti, L. St. Julien, J. Ramon, and C. Carbon.** 1995. Intestinal elimination of sparfloxacin, fleroxacin, and ciprofloxacin in rats. Antimicrob. Agents Chemother. **39:**99–102.
28. **Rubinstein, E., L. St. Julien, J. Ramon, S. Dautrey, R. Farinoti, J.-F. Huneau, and C. Carbon.** 1994. The intestinal elimination of ciprofloxacin in the rat. J. Infect. Dis. **169:**218–221.
29. **Ruckdeschel, G., G. Vogler, K. Unertl, W. Ehret, and H. Scholl.** 1989. The effect of intravenous application of ciprofloxacin on the intestinal flora of healthy volunteers. Abstract, p. 2311–2312. *In* Proceedings of the 16th International Conference on Chemotherapy, Jerusalem.
30. **Scholl, H., K. Schmidt, and B. Weber.** 1987. Sensitive and selective determination of picogram amounts of ciprofloxacin and its metabolites in biological samples using high-performance liquid chromatography and photothermal post-column derivatization. J. Chromatogr. **416:**321–330.
31. **Sörgel, F., K. G. Naber, U. Jaehde, A. Reiter, R. Seelman, and G. Sigl.** 1989. Brief report: gastrointestinal secretion of ciprofloxacin. Evaluation of the charcoal model for investigations in healthy volunteers. Am. J. Med. **87**(5A)**:** 62–65.
32. **Staib, A. H., D. Beermann, S. Harder, U. Fuhr, and D. Liermann.** 1989. Absorption differences of ciprofloxacin along the human gastrointestinal tract determined using a remote-control drug delivery device (HF-capsule). Am. J. Med. **87**(5A)**:**66–69.
33. **Szabo, S.** 1991. The mode of action of sucralfate: the $1 \times 1 \times 1$ mechanism of action. Scand. J. Gastroenterol. **26:**7–12.
34. **Tanimura, H., S. Tominaga, F. Rai, and H. Matsumoto.** 1986. Transfer of ciprofloxacin to bile and determination of biliary metabolites in humans. Arzneim.-Forsch. **36:**1417–1420.
35. **van Saene, J. J. M., H. K. F. van Saene, J. N. Geitz, and C. F. Lerk.** 1988. Effects of ciprofloxacin on the intestinal flora. Rev. Infect. Dis. **10:**198.
36. **van Saene, J. J. M., H. K. F. van Saene, and C. F. Lerk.** 1986. Inactivation of quinolones by feces. J. Infect. Dis. **153:**999–1000. (Letter.)
37. **Viell, B., B. Krause, K.-H. Vestweber, S. Schaaf, and H. Scholl.** 1992. Transintestinal elimination of ciprofloxacin in humans—concomitant assessment of its metabolites in serum, ileum and colon. Infection **20:**324–327.
38. **Yuk, J. H., C. N. Nightingale, and R. Quintiliani.** 1989. Ciprofloxacin levels when receiving sucralfate. JAMA **262:**901. (Letter.)
39. **Zeiler, H.-J., U. Petersen, W. Gau, and H. J. Ploschke.** 1987. Antibacterial activity of the metabolites of ciprofloxacin and its significance in the bioassay. Arzneim.-Forsch. **37:**131–134.