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Concentration of Pefloxacin in Feces during Infection Prophylaxis in Neutropenic Patients

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Pefloxacin (400 mg twice daily) was administered orally for infection prophylaxis in neutropenic patients. Diffusible fecal pefloxacin concentration was determined by bioassay during 24 neutropenic periods. The median diffusible fecal pefloxacin concentration was 187 μg/g. This concentration was comparable with those found in volunteers following oral and intravenous administration of pefloxacin (400 mg twice daily) (median of 171 and 155 μg/g, respectively). From this study, it is concluded that pefloxacin administered orally results in a predictable high diffusible fecal concentration which leads to effective elimination of susceptible aerobic gram-negative bacilli from the colonic flora.

Fluorinated carboxyquinolones are widely used for infection prophylaxis in patients with severe neutropenia (2, 4). These agents have a broad spectrum of activity against aerobic gram-negative bacilli (GNB) (including *Pseudomonas aeruginosa*) and are effective in preventing infections by gram-negative organisms (1, 5, 7, 10–12, 18).

Long-term prophylaxis of infection in patients with neutropenia may be achieved by elimination of potentially pathogenic aerobic flora from the digestive tract (3). In order to be effective, antibiotics used for decontamination of the digestive tract must reach high and predictable concentrations in the bowel (15). It has been suggested that nonabsorbable antimicrobial agents are required for this purpose (4). In volunteers, however, we observed high antimicrobial activity of pefloxacin in feces after oral (almost complete resorption) and intravenous administration of pefloxacin (16, 17).

In the present study, we investigated the diffusible fecal concentration of pefloxacin and eradication of GNB from feces in neutropenic patients following oral administration. We compare these results with those of similar previous studies in healthy volunteers following oral and intravenous administration (16, 17).

During 24 periods of chemotherapy-induced neutropenia, prophylactic antibiotics, including pefloxacin (400 mg twice a day [BID] orally), fluconazole (50 mg orally), amphotericin B (450 mg BID orally), and trimethoprim (2%, as nasal ointment), were given to decontaminate the digestive tract.

All 13 patients (median age, 51 years; range, 49 to 76 years) were treated for a hematologic malignancy, and median duration of neutropenia (<500 neutrophils per μl) was 16 days (range, 9 to 35). During the prophylaxis, no salads were permitted. Fecal samples were taken at admission and twice weekly to determine the diffusible pefloxacin concentration and to perform viable counts of aerobic GNB.

The diffusible fecal concentration of pefloxacin was determined by an agar diffusion method. An undiluted aliquot of feces was put in a well (depth, 5 mm; diameter, 7 mm; volume, 0.77 ml) in a solid medium of Iso-Sensitest agar (300 ml; Oxoid, Basingstoke, United Kingdom) seeded with a strain of *Escherichia coli* (ATCC 25922). The MIC of pefloxacin for this strain is 0.25 μg/ml. The diameters of the inhibition zones were compared with the diameters of the inhibition zone around standard solutions of pefloxacin in normal saline in the same agar plate (mean of three samples). The concentration found in this way is called the diffusible fecal concentration. With this method, antimicrobial activities of pefloxacin and its active metabolites (norfloxacin) are measured. Sensitivity (with the ATCC strain used) is 2 μg/g or higher. The coefficient of variation is lower than 2% when the diffusible concentration is higher than 2 μg/g.

Microbial analyses were done by serial 1/10 dilutions of feces in thioglycolate medium (BBL no. 11720). One-microliter volumes of each dilution were inoculated onto solid media to isolate GNB (eosin methylene blue lactose sucrose agar; Merck no. 1347) and amoxicillin-resistant GNB (5% sheep blood in blood agar base [Oxoid no. CM854] with amoxicillin [10 μg/ml]). The solid media were also inoculated with 100-μl volumes of the first 1/10 dilutions of feces, lowering the detection limit to 100 microorganisms per gram of feces. A microtiter system with 23 determinants was used for determination of the gram-negative microorganisms (6), and the MICs of the antibiotics were determined for the organisms.

In the neutropenic patients, the median diffusible fecal pefloxacin concentration 2 days after the start of prophylaxis was 77 μg/g (range, 55 to 103 μg/g). During the 24 periods of neutropenia, which lasted from 9 to 35 days, the median diffusible pefloxacin concentrations over the days ranged from 61 to 247 μg/g (median, 187 μg/g [Fig. 1]).

The range in pefloxacin concentration was due to interpatient variation more than to intrapatient variation. For example, the patient with the lowest and the patient with the highest diffusible pefloxacin concentration had a range of 36 to 159 μg/g (median, 87; $n = 11$) and 260 to 887 μg/g (median, 405; $n = 5$), respectively.

All 24 periods of prophylaxis with pefloxacin resulted in elimination of the GNB from the colonic flora. Cultures taken in the first four days after starting pefloxacin were still positive in 44% (four of nine cultures); thereafter, all cultures taken were negative for GNB. Only one patient had three successive positive fecal cultures on days 21, 24, and 28 with different GNB on each occasion in low concentrations (10^2 to 10^3

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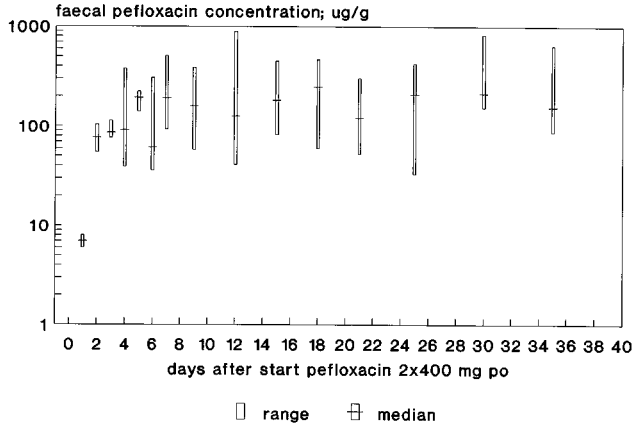

FIG. 1. Diffusible fecal pefloxacin concentration during 24 periods of neutropenia. Pefloxacin (400 mg) was administered orally BID for 9 to 35 days. Concentrations were measured twice weekly. Median and range are given in the figure.

CFU/g of feces). No infections by GNB were documented in the neutropenic patients.

These results are similar to the diffusible fecal concentration of pefloxacin in volunteers (16, 17). The oral administration of pefloxacin (400 mg BID) in six volunteers for 10 days resulted in a median diffusible fecal concentration of 171 μg/g (Fig. 2). During 5 days, of intravenous administration of pefloxacin at the same dose, median diffusible fecal concentration was 155 μg/g (five volunteers [Fig. 2]). Both oral and intravenous administration of the fluoroquinolone resulted in early and high diffusible faecal concentrations. On the first and second days after the discontinuation of the drug, diffusible fecal concentrations of pefloxacin were still high. This high and persistent concentration in feces is found in other studies (9).

The high diffusible fecal pefloxacin concentration is remarkable since the maximal concentration in plasma is 10 μg/ml at the doses used (8). Although there is biliary secretion of pefloxacin (biliary level two to five times higher than blood levels), this cannot explain why the concentration in feces is so much higher than in plasma (8). It has been shown, however, that quinolones are secreted in the bowel across the intestinal mucosa (13). This transepithelial elimination probably is an active transport (14).

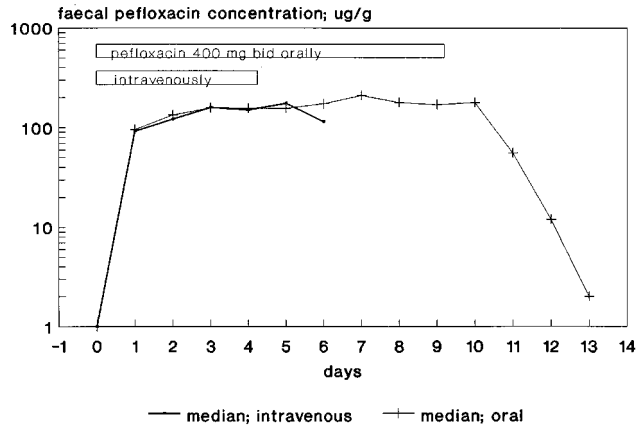

FIG. 2. Diffusible fecal pefloxacin concentration in healthy volunteers. Pefloxacin (400 mg BID) was administered orally for 10 days ($n = 6$) and intravenously for 5 days ($n = 5$).

The MICs for 90% of strains tested of pefloxacin for the aerobic GNB are 0.1 to 4.0 μg/ml for members of the family *Enterobacteriaceae* and 2 to 16 μg/ml for *P. aeruginosa* (8). The diffusible pefloxacin concentration in feces found in the present study is far above these MICs for 90% of strains tested. Therefore, strains which are resistant to the levels of pefloxacin in blood can still be eliminated from the digestive flora (15). This explains the efficacy of pefloxacin in decontaminating the gut.

In all patients, the aerobic gram-negative flora was eliminated within a week (twice-weekly sampling). During daily fecal sampling in volunteers, median elimination time of GNB was 3 days (range, 2 to 3 days) after oral pefloxacin and 2 days (range, 1 to >5 days) after intravenous administration (16, 17). After elimination of GNB from feces, one patient transiently acquired GNB in low concentration. These microorganisms could have been introduced with the food and just passed through the colon without growing out.

The variability in diffusible fecal pefloxacin concentration in patients was due especially to interpatient variation. The same was seen in the volunteers (16, 17). This variability can be due to duration of therapy, variation in resorption, variation in transepithelial elimination, inactivation due to interaction with other medication, or noncompliance. Also, feces volume affects the diffusible fecal pefloxacin concentration (unpublished data). In the patients, we did not find a correlation between comedication (including antimicrobial agents) and diffusible fecal concentration of pefloxacin. Despite the wide range of diffusible fecal pefloxacin concentration in the neutropenic patients, all levels were far above the usual MICs for 90% of strains of tested aerobic GNB.

We concluded that pefloxacin administered orally or intravenously results in comparable high diffusible concentrations in feces which exceed levels in blood by 15 to 25 times. This explains the efficacy of pefloxacin in eliminating the GNB from the digestive tract. In patients not able to take oral medication, decontamination of the bowel of GNB can be achieved by intravenous administration of pefloxacin.

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