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Effect of Broad-Spectrum Parenteral Antibiotics on Composition of Intestinal Microflora of Humans

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We compared the effects of four β-lactam drugs with widely differing antibacterial and pharmacological properties on the composition of the intestinal flora. Cefoxitin, piperacillin, cefoperazone, and aztreonam were given intravenously for 9 days to healthy volunteers. Cefoperazone reduced the numbers of aerobic and anaerobic bacteria to undetectable levels. At the other extreme, cefoxitin had little effect on the normal flora. Aztreonam markedly reduced the numbers of aerobes, whereas piperacillin had a variable effect on both aerobic and anaerobic bacteria. There was extensive overgrowth of enterococci in subjects given cefoxitin or aztreonam, which have little activity against this species, and of yeasts in subjects given cefoperazone or piperacillin. Cefoperazone reached concentrations of 2,727 to 8,840 μg/g in the feces, whereas the other agents were generally undetectable. These results show that the new β-lactam antibiotics produce widely varying effects on the fecal microflora after parenteral administration and that these effects are consistent with the antibacterial and pharmacological properties of the drugs.

Antibiotics administered parenterally may have important effects on the composition of the fecal microflora (5, 13–15, 18, 19, 22). Several of the new β-lactam drugs have been shown to produce significant derangements (2, 3, 5, 19, 23, 24), presumably because they are secreted into the bile in appreciable concentrations (3, 21). A number of adverse reactions to antibiotics have been related to changes in the fecal microflora including diarrhea, overgrowth of *Clostridium difficile* and fungi, the selection of antibiotic-resistant strains, and a diminution in so-called colonization resistance. Studies in animals have documented the phenomenon of colonization resistance (1, 25–27) and have related it to the anaerobic component of the fecal microflora (17, 28, 30); however, other studies have suggested that facultative gram-negative rods are important in this regard (9, 10, 16).

Despite the potential importance of these effects, there are few comparative studies of the impact of various parenteral antibiotics on the fecal microflora (5, 23), and none which proves that there is a phenomenon of colonization resistance in humans. Therefore, we investigated these issues by administering four representative β-lactam antibiotics with differing antibacterial and pharmacological properties to healthy volunteers. The antibiotics chosen were aztreonam, a monobactam which has no activity against anaerobic or gram-positive bacteria (11); cefoperazone, a broad-spectrum cephalosporin with an exceptionally high degree of biliary excretion (4, 20, 21); piperacillin, a broad-spectrum penicillin (8); and cefoxitin, a cephamycin compound with activity against aerobic and anaerobic bacteria (4). In the present paper we report the effects of these agents on the normal fecal microflora of volunteers.

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MATERIALS AND METHODS

Subjects. Twenty healthy volunteers, 15 males and 5 females, between 20 and 38 years of age, were selected for the study. Subjects were excluded if they had a history of chronic disease or drug allergy or had been treated with an antibiotic within 2 months before entry. The study was approved by the Human Investigation Review Committee, and all subjects gave informed, written consent.

Drug administration. Four volunteers were randomized to each of the following treatment groups: aztreonam, 2 g every 6 h; cefoperazone, 2 g every 12 h; cefoxitin, 2 g every 6 h; and piperacillin, 3 g every 4 h. All drugs were administered intravenously for a 9-day period. The subjects remained in the Clinical Study Unit of the New England Medical Center during the period of antibiotic administration and for 1 day thereafter. Four subjects served as untreated controls for the studies of colonization resistance which will be discussed in a separate paper (M. Barza, M. Guiliano, N. V. Jacobus, and S. L. Gorbach, submitted for publication).

Drug assays. Peak and trough antibiotic concentrations were measured in serum obtained on days 3 and 6. Antibiotic concentrations in the feces were measured in samples obtained on days 9 and 12 of treatment. The concentrations were determined by a microbiological agar-diffusion method.

Safety evaluation. Complete blood counts and serum chemistry profile (blood urea nitrogen, creatinine, electrolytes, total bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase) were performed for each subject before treatment and on day 9 of treatment. Bleeding times and coagulation studies were conducted before treatment and on days 3, 6, and 9 of treatment. If any test was abnormal during treatment it was repeated after the end of treatment until it returned to normal.

Collection of stool specimens for microbiological studies. Stool specimens were collected within 1 week before antibi-

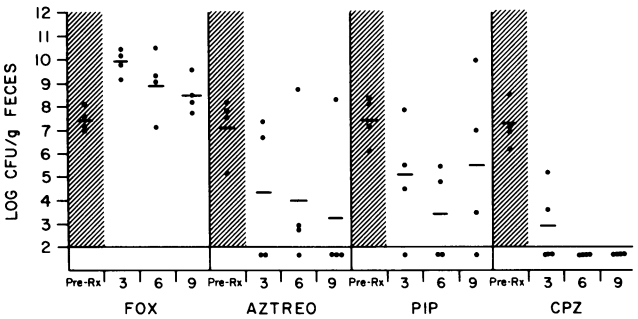

FIG. 1. Effects of the four antibiotics on *Enterobacteriaceae*. All the counts are expressed in $\log_{10}$ CFU per gram (dry weight). Counts below 2 $\log_{10}$ were not detectable. Shaded areas; Counts before treatment. FOX, Cefoxitin; AZTREO, aztreonam; PIP, piperacillin; CPZ, cefoperazone.

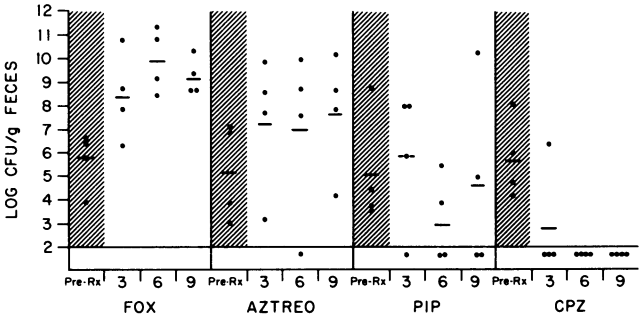

FIG. 2. Effects of the four antibiotics on enterococci. All the counts are expressed in $\log_{10}$ CFU per gram (dry weight). Counts below 2 $\log_{10}$ were not detectable. Shaded areas; Counts before treatment. Abbreviations are defined in the legend to Fig. 1.

otic treatment, on days 3, 6, and 9 of treatment, after antibiotics were discontinued (on days 12 and 14), and then twice weekly until the stool cultures returned to their pretreatment composition.

Processing of fecal specimens. All specimens were taken immediately to the laboratory and processed within 1 h. A 1-g sample of the specimen was transported to an anaerobic chamber, diluted 10-fold in phosphate-buffered saline plus 1% gelatin, and emulsified in a Vortex mixer. Serial 10-fold dilutions were made in phosphate-buffered saline plus gelatin. Samples of 0.1 ml of selected dilutions were plated on the following media for the purposes indicated: brucella blood agar with vitamin K and hemin for total aerobic and anaerobic counts; MacConkey agar for enumeration of members of the family *Enterobacteriaceae*; kanamycin-esculin-azide agar for enumeration of enterococci; salt-mannitol agar for enumeration of staphylococci; pseudomonas agar with C-N supplement (200 mg of cetrimide per liter and 15 mg of nalidixic acid per liter) for enumeration of pseudomonas; Mycosel agar for enumeration of yeasts; kanamycin-vancomycin-laked blood agar for enumeration of the *Bacteroides fragilis* group; and cycloserine-cefoxitin-egg yolk-fructose agar for enumeration of *C. difficile*. MacConkey agar no. 3, pseudomonas agar base with C-N, and the fructose agar base for *C. difficile* were obtained from Oxoid, Basingstoke, Hampshire, England. Mycosel agar was purchased from BBL Microbiology Systems, Cockeysville, Md. Brucella agar base, bile-esculin-azide agar, and salt-mannitol agar were provided by GIBCO Diagnostics, Madison, Wis.

Plates were incubated at 37°C for 24 h for aerobic cultures or for 48 h in an anaerobic chamber for anaerobic cultures. Plates that showed 30 to 300 colonies were used for bacterial counts. Colonies growing anaerobically on laked blood-kanamycin-vancomycin agar were verified as strict anaerobes by their failure to grow on replicate plates in an oxygen-containing atmosphere. *Enterobacteriaceae* and yeasts were further identified biochemically with the API 20E and API 20C test kits (Analytab Products, Plainview, N.Y.), respectively. The lowest detectable number of organisms with these methods is 2.0 $\log_{10}$ per g of feces.

Assay of cytotoxin. All stool specimens were assayed for *C. difficile* cytotoxin by a tissue culture assay with neutralization by specific antitoxin (6).

Statistical analysis. The Pearson correlation coefficient was used to analyze the experimental data. A P value of <0.05 was considered significant.

RESULTS

Effect on normal fecal flora. The effect of the four antibiotic regimens on the fecal counts of *Enterobacteriaceae* is shown in Fig. 1. Cefoperazone had the most striking effect, reducing the counts to undetectable levels by day 6 of treatment in all four subjects. Treatment with aztreonam caused a progressive decline in counts of *Enterobacteriaceae* to undetectable levels in three subjects; however, there was no appreciable change in the fourth subject. There was a modest overall reduction in counts with piperacillin, but this was highly variable from subject to subject. Treatment with cefoxitin caused a transient increase in counts in all four subjects.

The influence of treatment on the counts of enterococci is shown in Fig. 2. Cefoperazone caused a reduction to undetectable levels in all four subjects. Treatment with piperacillin produced a variable effect. Administration of cefoxitin and aztreonam was associated with a consistent increase in enterococcal counts ranging as high as 6 to 7 logs.

The impact of antibiotic treatment on the anaerobic flora is shown in Fig. 3. The predominant organisms were members of the *B. fragilis* group. Cefoperazone caused a reduction in counts to undetectable levels by day 6 of treatment in all four subjects. Treatment with cefoxitin and aztreonam did not influence the counts of these bacteria. The effect of piperacillin was highly variable but was striking in only one subject in whom counts were reduced to undetectable levels.

The drug with the greatest impact on the fecal counts of

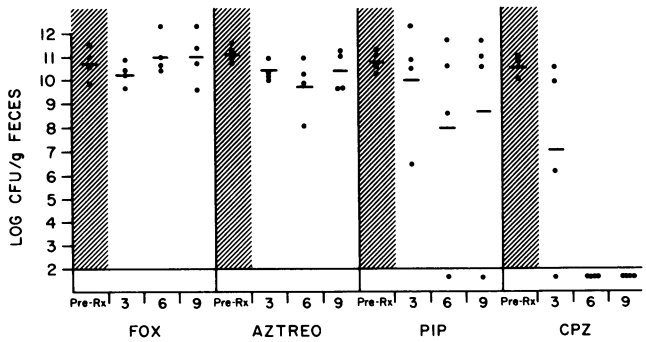

FIG. 3. Effects of the four antibiotics on anaerobes. All the counts are expressed in $\log_{10}$ CFU per gram (dry weight). Counts below 2 $\log_{10}$ were not detectable. Shaded areas, Counts before treatment. Abbreviations are defined in the legend to Fig. 1.

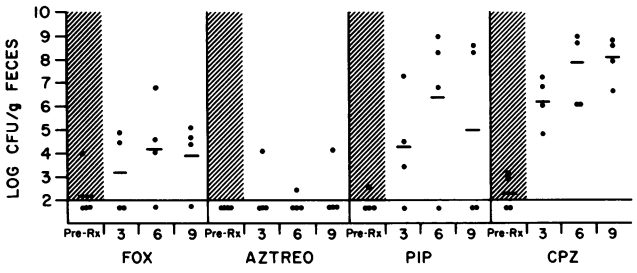

FIG. 4. Effects of the four antibiotics on yeasts. All the counts are expressed in $\log_{10}$ CFU per gram (dry weight). Counts below 2 $\log_{10}$ were not detectable. Shaded areas; Counts before treatment. Abbreviations are defined in the legend to Fig. 1.

yeasts was cefoperazone (Fig. 4); all four volunteers had striking increases in counts, ranging from 5.8 to 7.3 logs. Three of four subjects in the cefoxitin and piperacillin groups had appreciable counts of yeasts in the stool. Only one subject treated with aztreonam had a detectable number of yeasts in the feces. Most of the fungal isolates were *Candida albicans*; however, *Torulopsis glabrata* and *Candida tropicalis* were recovered in a few instances. There was a significant ($P < 0.01$) inverse correlation between the log of the maximum increase in yeasts and the log of the maximum decrease in anaerobes (Fig. 5).

There was no significant change in the fecal counts of staphylococci in any subject. *Pseudomonas aeruginosa* was not detected in the pretreatment fecal flora of any of the volunteers. All cultures and toxin assays for *C. difficile* were negative.

The fecal flora returned to its pretreatment composition by approximately 1 week after the last administration of cefoxitin, piperacillin, and aztreonam and approximately 2 weeks after the last dose of cefoperazone.

Antibiotic concentrations. The peak levels in serum (micrograms per milliliter) varied from 44 to 177 for cefoperazone, from 12 to 154 for cefoxitin, from 23 to 90 for piperacillin, and from 41 to 283 for aztreonam and were somewhat higher on day 6 than on day 3 of treatment (Table 1). The concentrations of antibiotics in feces are shown in Table 2. Cefoperazone reached extremely high levels on day 9 and was still detectable in appreciable concentrations 3 days after the end of treatment (day 12). One subject in each of the other three groups had detectable antibiotic in the feces on day 9 of treatment.

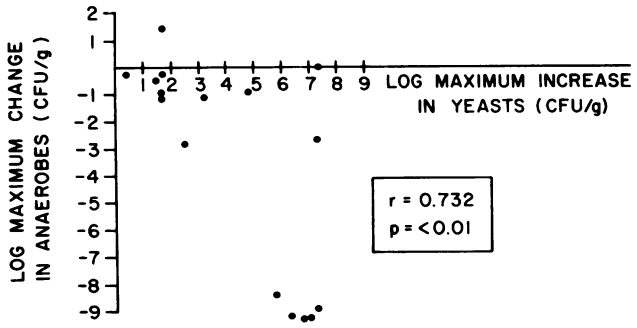

FIG. 5. Correlation between decrease in the counts of anaerobes and increase in the counts of yeasts (Pearson's correlation coefficient *r*).

TABLE 1. Mean peak and trough concentrations of the antimicrobial drugs in serum

Drug	Mean concn (μg/ml)			
	Day 3		Day 6	
	Peak	Trough	Peak	Trough
Cefoperazone	68	0.9	97	1.6
Cefoxitin	41	0.3	60	0.1
Piperacillin	45	15	68	9
Aztreonam	78	16	120	20

To determine the spontaneous initial rate of breakdown of antibiotic in the feces, stool from a healthy person who had received no antibiotics recently was incubated with each of the study drugs at concentrations of 100 and 1,000 μg/g of feces and was assayed 6 and 24 h after incubation at 37°C. The drugs were quite stable (less than 50% decrease in concentration) in the stool for 6 h except that cefoperazone at the lower concentration became undetectable over this interval. By 24 h, the concentration of piperacillin and cefoperazone had decreased by at least 99%, and the concentration of aztreonam had decreased by 90% or more, whereas the concentration of cefoxitin remained relatively stable.

Reactions to drug administration. Two subjects in the cefoperazone group and two in the piperacillin group had diarrhea (three or more loose stools per day) during treatment, and one developed fever and a rash on day 8 of treatment with cefoperazone; these reactions remitted within a day or two after stopping the drug. One subject had a disulfiram-like reaction which persisted for 7 days after the end of cefoperazone treatment. One aztreonam recipient and one cefoxitin recipient had abnormalities of liver function tests during treatment; these returned to normal within 1 week after treatment. Aztreonam was discontinued in one volunteer on day 8 of treatment because of a prolongation in the bleeding time; in another subject, the treatment was interrupted for four doses on day 6 for the same reason. In

TABLE 2. Drug concentrations in stool during and after treatment

Regimen	Subject	Concn (μg/ml)	
		Day 9	Day 12
Cefoperazone	1	3,200	7
	2	8,840	1,010
	3	5,340	1,800
	4	2,727	304
Cefoxitin	1	ND[a]	ND
	2	8	ND
	3	ND	ND
	4	ND	ND
Piperacillin	1	ND	ND
	2	108	ND
	3	ND	ND
	4	ND	ND
Aztreonam	1	ND	ND
	2	ND	ND
	3	23	ND
	4	ND	ND

[a] ND, Not detectable, i.e., cefoxitin, aztreonam, or cefoperazone, ≤5 μg/ml; piperacillin, ≤80 μg/ml.

TABLE 3. Effect of antibiotic regimen on composition of the fecal microflora[a]

Regimen	Drug concn in feces	*Enterobacteriaceae*	Anaerobes	Enterococci	Yeasts
Cefoxitin	Low	↑	0	↑↑	↑
Aztreonam	Low	↓↓	0	↑	0
Piperacillin	Low	↓↓	↓	↓	↑↑
Cefoperazone	High	↓↓↓	↓↓↓	↓↓↓	↑↑↑

[a] 0, Maximum change of 0 to 2 logs; ↑ or ↓, maximum change of 2 to 4 logs; ↑↑ or ↓↓, maximum change of 4 to 6 logs; ↑↑↑ or ↓↓↓, maximum change >6 logs.

no subject did the prothrombin time change by more than 1.5 s from the base line during the course of the study. No subject developed a superinfection during the study.

DISCUSSION

The potential impact of parenterally administered broad-spectrum antibiotics on the intestinal flora has been recognized for many years. The development of a number of highly potent new β-lactam drugs has rekindled interest in this area. Studies with sick patients and with healthy volunteers have shown that drugs such as cefoperazone and ceftriaxone have striking effects on the composition of the fecal microflora, presumably because the drugs are highly potent and are excreted extensively in the bile (2, 3, 5, 19, 21).

There may be a number of consequences of antibiotic-induced derangements in the intestinal microflora. First, diarrhea may result; this may occur with any of the drugs but may be somewhat more common with cefoperazone (2, 19). Second, there may be overgrowth of one or another species of microorganism present before treatment was started. Examples include *C. difficile* (18), which may cause colitis, and various fungi, which may produce systemic infection in certain patients. Third, as a result of the continuous exposure of high numbers of microorganisms to antibiotic, there may be induction of β-lactamases and an increase in the numbers of resistant bacteria (22). Fourth, the striking reduction in the normal bacterial flora could conceivably lead to a diminution in colonization resistance, i.e., resistance to colonization by exogenous microorganisms (1, 9, 10, 16, 17, 25–28, 30).

In this study, we compared the effects of representative new β-lactam antibiotics with differing antibacterial and pharmacological properties on the composition of the intestinal microflora. The impact of these drugs on the acquisition of new colonizing organisms, i.e., colonization resistance, the emergence of resistant strains, and the induction of β-lactamase, will be reported elsewhere (Barza et al., submitted). Although there are a number of reports of the effect of individual drugs on the fecal microflora, there are few if any comparing the effects of a variety of antibiotics in a relatively homogeneous population. To reduce the number of variables such as disease and recent exposure to antibiotics which might affect the outcome, we studied healthy volunteers rather than sick patients.

There were marked differences among the antibiotic regimens in their impact on the normal fecal flora (Table 3). Treatment with cefoperazone had the most dramatic effect, reducing the numbers of both the aerobic (*Enterobacteriaceae*) and anaerobic (primarily *B. fragilis*) flora to undetectable levels. At the other extreme, treatment with cefoxitin had virtually no effect on either component. The administration of aztreonam reduced the counts of aerobes only, whereas treatment with piperacillin produced variable effects on both components of the microflora. Although we studied only a small number of subjects, our results are generally consistent with those reported in noncomparative investigations of piperacillin (15), cefoxitin (18), and cefoperazone (2, 19). In one study of aztreonam given intravenously (12) the effect on anaerobes, particularly *B. fragilis*, was greater than that which we found, but in another trial in which the drug was given intravenously (13) and a third trial in which it was administered orally (7) the results were similar to those in our subjects.

These effects on the aerobic and anaerobic microflora can be explained by a combination of the antibacterial and pharmacological properties of the drugs. Cefoperazone produced extremely high fecal concentrations, consistent with the fact that up to 75% of a dose is eliminated in the bile (21); this pharmacological property, combined with the broad spectrum of activity of cefoperazone, led to the eradication of most of the normal flora. Ceftriaxone, which is also excreted extensively in the bile, appears to have similar effects on the fecal microflora (3, 5). Piperacillin, cefoxitin, and aztreonam produced much lower concentrations than did cefoperazone in the feces, as has been reported by others (15, 18, 24). Nevertheless, the concentrations of aztreonam were sufficient to affect aerobes and those of piperacillin were sufficient to affect both aerobes and anaerobes in selected individuals, consistent with the antibacterial spectra of these agents.

The high concentrations of cefoperazone were not related to unusual stability of this drug in the stool; indeed, cefoxitin was the most stable and aztreonam was the next most stable drug in the feces, whereas piperacillin and cefoperazone were degraded by more than 99% in 24 h. Others have reported aztreonam to be fairly stable in feces (29).

Two components of the microflora tended to overgrow during treatment, namely, enterococci and yeasts. Enterococci tended to overgrow in volunteers treated with cefoxitin or aztreonam, agents which have no appreciable activity against this species; by contrast, yeasts overgrew in subjects treated with cefoperazone or piperacillin, agents which are active against enterococci. However, as opposed to our results, Alestig and colleagues found an increase in counts of enterococci but not in yeasts during the administration of cefoperazone (2). Other investigators have reported increases in fecal counts of enterococci when aztreonam (7) or cefoxitin (18) was administered.

The extent of overgrowth of yeasts during antibiotic treatment was striking. These organisms were detectable in the stools of 4 of 16 patients before antibiotic treatment and 10 of 16 after antibiotic treatment. In subjects treated with cefoperazone, the normal flora was essentially replaced by yeasts. Although the yeasts were presumably present in undetectable numbers before antibiotic treatment, some strains may have been acquired from the environment during treatment. There was a significant correlation between the increase in numbers of yeasts and the decrease in numbers of anaerobes during treatment. This does not necessarily indicate that anaerobic bacteria inhibit the growth of yeasts in the intestine but may simply show that when the dominant aerobic and anaerobic components of the microflora are suppressed, other microorganisms, particularly enterococci and yeasts, will overgrow to fill the "vacuum." Occasionally, other species such as staphylococci or *C. difficile* may fulfil this role. Presumably, the final pattern of overgrowth will be determined by the antibacterial spectrum of the drug

being given and the composition of the fecal microflora before treatment.

Taken together, these data show a variable effect of the new β-lactam antibiotics on the composition of the fecal microflora. In general, the alterations can be related to a combination of the pharmacological properties, particularly the extent of biliary excretion, and the antibacterial properties of the specific agent.

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