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Effect of Amoxicillin-Clavulanate and Cephradine on the Fecal Flora of Healthy Volunteers Not Exposed to a Hospital Environment

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A 7-day course of either cephradine or amoxicillin-clavulanate treatment caused no significant change in fecal flora composition, except that staphylococci were virtually eliminated in both groups. Some amoxicillin-resistant coliforms were isolated after treatment in both groups, but cephradine- or amoxicillin-clavulanate-resistant coliforms were rarely isolated.

Cephradine and amoxicillin-clavulanate, broad-spectrum antibiotics which can be taken orally, are being used more frequently in the treatment of urinary infections. In view of the apparent lack of related information available, we undertook a study to determine side effects and changes in the fecal flora composition in volunteers given a 7-day course of cephradine or amoxicillin-clavulanate at the recommended therapeutic doses.

Twelve healthy volunteers (four males, eight females), none of whom worked in or had attended a hospital during the preceding 6 months, were randomly assigned to take either 1 g of cephradine every 12 h (subjects 1 to 6) or 250 mg of amoxicillin plus 125 mg of clavulanate every 8 h (subjects 7 to 12). Volunteers recorded details of bowel movements and any intestinal side effects. A specimen of feces was collected before treatment, as soon as possible after the end of treatment, and 1 week after the end of treatment. Quantitative cultures were made from homogenates of feces by techniques described elsewhere (2). Strains were tested for susceptibility to cephradine, amoxicillin-clavulanate, and amoxicillin by disk diffusion. Antibiotic in the feces taken at the end of treatment was estimated by hole-plate assay using *Micrococcus luteus* NCTC 8340 as indicator organism for amoxicillin, *Klebsiella aerogenes* NCTC 11228 as indicator organism for clavulanate, and *Bacillus subtilis* ATCC 6633 as indicator organism for cephradine.

Staphylococci had virtually disappeared from the feces on the last day of treatment with either antibiotic, and counts of nonfecal streptococci were significantly decreased as a result of amoxicillin-clavulanate treatment. No other significant changes were found; in particular, total counts of coliforms, fecal streptococci, and anaerobes were unaffected by either antibiotic. Only small numbers of yeasts were isolated, and there was no overgrowth as a result of treatment with either antibiotic. Results are summarized in Table 1.

A cephradine-resistant coliform was found only in feces from subject 6 (who had taken cephradine) (Table 2). This *Escherichia coli* strain was resistant to sulfonamide, trimethoprim, tetracycline, cephradine, amoxicillin, and amoxicillin-clavulanate. It had been present in small numbers in the pretreatment specimen. There was some increase in the incidence of amoxicillin resistance in both treatment groups but no increase in the incidence of resistance to amoxicillin-clavulanate. A total of 94 strains of obligate anaerobes were isolated. Most were susceptible to cephradine (75%), amoxicillin (88%), and amoxicillin-clavulanate (98%); there were no obvious changes in patterns of susceptibility as a result of either treatment. No antibiotic activity was found in 1:10 dilutions of feces taken immediately after the end of treatment in any of the volunteers. Taking into account the minimum limits of detection of the various assays, maximum concentrations of the various antibiotics were as follows: cephradine, <60 μg/g; amoxicillin, <0.3 μg/g; clavulanate, <1.5 μg/g.

TABLE 1. Quantitative effects of 7-day treatment with cephradine or amoxicillin-clavulanate on fecal flora composition in 12 volunteers

Drug and bacterial species or type	Log_{10} mean bacterial count (standard error)/g of feces		
	Pretreatment	Immediately posttreatment	7 days posttreatment
Cephradine			
Coliform[a]	7.70 (0.54)	6.34 (0.68)	6.77 (0.73)
Staphylococci	2.73 (0.59)	0.63[b] (0.54)	1.04 (0.66)
Streptococci	4.72 (1.05)	2.67 (1.2)	4.83 (1.1)
Fecal streptococci	3.15 (0.99)	3.62 (0.81)	4.43 (0.97)
Lactobacilli	5.14 (1.32)	7.2 (1.2)	8.33 (0.37)
Anaerobes[c]	9.2 (0.43)	9.0 (0.22)	9.8 (0.28)
Amoxicillin-clavulanate			
Coliform[a]	7.2 (0.46)	7.89 (0.67)	6.68 (0.9)
Staphylococci	3.48 (1.35)	<1[b]	1.81 (0.81)
Streptococci	4.64 (0.98)	1.82[d] (1.22)	0.95[d] (0.95)
Fecal streptococci	3.34 (1.6)	4.25 (1.57)	6.23 (1.44)
Lactobacilli	4.78 (1.51)	8.06 (0.77)	7.96 (0.74)
Anaerobes[c]	8.21 (0.42)	8.98 (0.42)	9.57 (0.27)

[a] Nature and susceptibilities of these strains are given in Table 2.
[b] Significantly lower than pretreatment and 7-day posttreatment values.
[c] *Bacteroides fragilis* was the predominant anaerobic species in 19 of the 36 specimens.
[d] Significantly lower than pretreatment value.

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TABLE 2. Effect of 7-day treatment with cephradine or amoxicillin-clavulanate on the nature and susceptibility of predominant fecal coliforms in 12 volunteers

Drug taken and volunteer no.	Predominant coliform (susceptibility pattern)[a]		
	Pretreatment	Immediately posttreatment	7 days posttreatment
Cephradine			
1	*E. coli* (SSS)	*E. coli* (SRS)	*E. coli* (SRR)[b] *E. coli* (SSS)[b]
2	*Citrobacter freundii* (SRS)	*E. coli* (SRS)	*E. coli* (SSS)
3	*E. coli* (SSS)	*E. coli* (SSS)	*E. coli* (SSS)
4	*C. freundii* (SSS)	*E. coli* (SSS)	*E. coli* (SSS)
5	*E. coli* (SSS)	*E. coli* (SSS)	*E. coli* (SSS)
6	*E. coli* (SSS)	*E. coli* (RRR)	*E. coli* (RRR)
Amoxicillin-clavulanate			
7	*E. coli* (SSS)	*Klebsiella oxytoca* (SRS)	*K. oxytoca* (SRS)
8	*E. coli* (SSS)	*E. coli* (SRS)	*E. coli* (SSS)
9	*E. coli* (SSS)	*K. oxytoca* (SRS)	*C. freundii* (SRS)
10	*E. coli* (SSS)	*E. coli* (SSS)	*E. coli* (SSS)
11	*E. coli* (SSS)	*E. coli* (SSS)	*E. coli* (SSS)
12	*E. coli* (SSS)	*E. coli* (SRS)	*E. coli* (SSS)

[a] S, Susceptible, and R, resistant to cephradine, amoxicillin, and amoxicillin-clavulanate, respectively, by disk diffusion.
[b] Equal numbers of these two strains.

Subjects taking cephradine had bowel movements 1.35 (standard deviation, 0.36) times per day while taking the antibiotic; for those taking amoxicillin-clavulanate, the corresponding figure was 1.13 (standard deviation, 0.45) times (not significantly different). There was no difference in looseness of stools in either group. Two subjects in each group reported passing feces more often while on treatment than normally. No volunteer reported flatus, abdominal discomfort, or (when appropriate) vaginal candidiasis.

Neither cephradine nor amoxicillin-clavulanate had a major effect on the compositions of gut flora. For cephradine, this can be explained by complete absorption from the small bowel, which is supported by the lack of antibiotic activity in fecal homogenates. We cannot, however, explain the lack of effect of amoxicillin-clavulanate in these terms, because amoxicillin is not completely absorbed from the gut, and, when it is given alone, resistant coliforms emerge (8, 9).

Other workers have reported more substantial changes in fecal flora composition after administration of the closely related antibiotic cephalexin. Gaya et al. (6) found that hospital patients given cephalexin acquired *Pseudomonas aeruginosa* in the stool, and Hartley et al. (7) reported that coliforms other than *E. coli* (some cephalexin resistant) predominated in the flora after cephalexin treatment. Sutter and Finegold (10) made similar findings. Asquith and Lacey and Lacey et al. (1, 8) observed more selection of cephradine-resistant coliforms after cephradine administration than we did. However, most subjects studied previously were in-patients, and merely being admitted to a hospital is known to have a profound effect on the composition of fecal flora, even if antibiotics have not been used (5).

Mittermayer (9), using a different dosage of amoxicillin-clavulanate (500 plus 125 mg, respectively, every 8 h), reported selection of coliforms resistant to amoxicillin-clavulanate. This is contrary to our findings and may be due to the different regimen.

Our results are encouraging with respect to the long-term prospects for the use of cephradine and amoxicillin-clavulanate in urinary infections. The lack of selection of resistant strains contrasts with the situation found with some other antibiotics that have recently been widely used. For example, organisms causing urinary infections in patients attending our Urinary Infection Clinic and in the general population served by our laboratory show increasing incidences of resistance to trimethoprim and amoxicillin (3). This finding is probably associated with the ability of these two antibiotics to select for resistant bowel flora. Amoxicillin does this after a course of therapy as short as only 7 days, whereas trimethoprim may take longer to select for resistant coliforms (4). In a recent clinical trial in which cephradine was given prophylactically for 12 months (unpublished data), we observed neither emergence of resistant species nor selection for intrinsically resistant species.

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