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Comparison of Cefoxitin and Cephalothin Therapy of a Mixed *Bacteroides fragilis* and *Fusobacterium necrophorum* Infection in Mice

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Cefoxitin, a β-lactamase-resistant cephalosporin, was found to be more effective than cephalothin against an experimental mixed infection containing *Bacteroides fragilis* and *Fusobacterium necrophorum*.

In a recent study of a mixed anaerobic infection with *Bacteroides fragilis*, a gram-negative human pathogen, and *Fusobacterium necrophorum*, a gram-negative animal pathogen, we found that penicillin-resistant *B. fragilis* strains were capable of protecting a penicillin-susceptible *F. necrophorum* strain from penicillin therapy. If penicillinase production by *B. fragilis* is responsible for this protection, a β-lactamase-resistant antibiotic should be more effective against the mixed infection than a β-lactamase-susceptible antibiotic of similar properties. We therefore compared the efficacy of cefoxitin, a 7α-methoxy-cephalosporin reported to be resistant to inactivation by most gram-negative β-lactamases (4), with cephalothin, a cephalosporin which is susceptible to inactivation by β-lactamases produced by species of gram-negative rods.

Details of the mixed infection have been described (2). Bacterial strains were obtained from the culture collection of the Virginia Polytechnic Institute Anaerobe Laboratory. A mixture of *B. fragilis* (VPI 3625) and *F. necrophorum* (ATCC 27852, VPO 6054A) was injected subcutaneously in the groin area of mice. The *B. fragilis* strain, a human clinical isolate, had been found previously to be able to protect *F. necrophorum* from penicillin doses as high as 2,000 mg/kg. A pure *F. necrophorum* infection (5) was also used to determine the in vivo efficacy of cefoxitin and cephalothin against *F. necrophorum* alone. Cefoxitin (Merck & Co., Inc., Rahway, N.J.) was dissolved in distilled water and injected intraperitoneally at 4, 20, 28, 44 and 52 h after bacterial challenge. The same procedure was followed for cephalothin injections. Ten mice were tested at each twofold dilution of antibiotic. At least five dilutions of each antibiotic were tested. Mortality was determined by counting the number of mice dead within 21 days. Mean effective dosage values were calculated by the method of Bliss (1). Duplicate determinations of mortality at all dilutions were made for cephalothin, but due to the limited amount of cefoxitin available, duplicate determinations could only be made with this drug for the three concentrations nearest the mean effective dosage.

Minimal inhibitory concentration (MIC) values were determined using a broth dilution method (3). Both cefoxitin and cephalothin had a minimal inhibitory concentration of 0.5 μg/ml against *F. necrophorum*. Cephalothin had a slightly higher minimal inhibitory concentration value (128 μg/ml) against *B. fragilis* (3625) than cefoxitin (64 μg/ml).

Results of cefoxitin and cephalothin therapy of the pure *F. necrophorum* infection are shown in Table 1. Both cefoxitin and cephalothin were approximately equally effective against the pure *F. necrophorum* infection, although the required dosage levels for both antibiotics were high. Cefoxitin, however, was much more effective than cephalothin against the mixed infection.

The greater effectiveness of the β-lactamase-resistant drug cefoxitin against the *B. fragi-*

TABLE 1. *Comparison of cefoxitin and cephalothin mean effective dosage (ED_{50}) values for a pure F. necrophorum infection and a mixed B. fragilis-F. necrophorum infection in mice*

Infection	ED_{50} values (mg/kg per dose)	
	Cephalothin	Cefoxitin
F. necrophorum	291 (±50)[a]	121 (±23)
Mixed	>2,000	263 (±52)

[a] Standard deviation.

lis-F. necrophorum mixed infection as compared to the β-lactamase-susceptible drug cephalothin indicates that β-lactamase production by *B. fragilis* plays an important part in the ability of *B. fragilis* to protect *F. necrophorum* from penicillin and cephalothin in vivo.

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