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Comparative In Vitro Activity of Five Cephalosporin Antibiotics Against Salmonellae†

LARRY J. STRAUSBAUGH,[1]†† ISIS A. MIKHAIL, AND DAVID C. EDMAN[2]

Clinical Tropical Medicine[1] and Bacteriology Departments,[2] U.S. Naval Medical Research Unit No. 3, Cairo, Arab Republic of Egypt

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The in vitro activities of five cephalosporin antibiotics against 121 strains of salmonellae were compared. Cefamandole and cefaclor were more potent than cefazolin, and these three drugs were more active than cephalothin and cephalexin.

Antibiotic resistance has been frequently observed in clinical isolates of salmonellae during the last decade. The chloramphenicol-resistant strains of *Salmonella typhi* isolated during the 1972 epidemic of typhoid fever in Mexico have attracted the most attention, but the problem has involved other countries and other species of salmonellae (1, 3–5, 8, 9, 11, 12). The appearance of resistant strains has revived interest in the susceptibility of salmonellae to other antimicrobial agents including the cephalosporin antibiotics (1, 10, 14). Although the older cephalosporin antibiotics such as cephalothin and cephalexin have not proved to be useful in the therapy of *Salmonella* infections, the potential role of the newer cephalosporins has not been determined. The purpose of this study was to compare the in vitro bactericidal activity of three relatively new cephalosporin derivatives—cefazolin, cefamandole, and cefaclor—against 121 strains of salmonellae isolated in Egypt with the activity of the two older agents, cephalothin and cephalexin.

The 121 *Salmonella* isolates included 67 strains of *S. typhi* and 54 strains of *S. paratyphi* A. All strains of *S. typhi* and 49 strains of *S. paratyphi* A were isolated between 1969 and 1977 from patients at the Abbassia Fever Hospital, Cairo, Arab Republic of Egypt. Five strains of *S. paratyphi* A were isolated in 1977 from school boys in Luxor, Egypt, during an epidemiological survey for bacteriuria. Fifty of the *S. typhi* strains were isolated from blood, 10 from urine, and 7 from stool. Thirty of the *S. paratyphi* A strains were isolated from blood, 23 from urine, and 1 from stool. The bacteria were isolated and identified by standard biochemical and serological procedures in the Bacteriology Department, U.S. Naval Medical Research Unit No. 3. None of these isolates were resistant to chloramphenicol or ampicillin as determined by the laboratory's routine disk diffusion susceptibility tests.

The minimal inhibitory concentrations (MIC) of the five cephalosporin antibiotics were determined by the agar-dilution method (15), using the inocula-replicating apparatus described by Steers and colleagues (13). Freshly prepared stock solutions of cefazolin, cefamandole, cefaclor, cephalothin, and cephalexin (supplied by Eli Lilly and Co., Indianapolis, Ind.) were diluted in soybean-casein digest agar (General Biochemicals, Chagrin Falls, Ohio) to produce test plates with drug concentrations of 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78, 0.39, and 0.19 μg/ml. The plates were inoculated with 10^4 colony-forming units of each strain, and the MIC values were read after 18 h of incubation at 37°C. The MIC was defined as the lowest concentration yielding no growth, a barely visible haze, or less than three discrete colonies (15).

Cefamandole and cefaclor demonstrated greater bactericidal activity against *S. typhi* than the older cephalosporins, but cefazolin demonstrated activity similar to that of cephalothin (Table 1). Cefamandole was slightly more potent than cefaclor. Ninety-two percent of the *S. typhi* strains were inhibited by 0.39 μg of cefamandole, whereas 97% were inhibited by 0.78 μg of cefaclor per ml. In contrast, a comparable measure of inhibition required 1.56 μg of cephalothin or cefazolin and 6.25 μg of cephalexin per ml.

All three of the newer cephalosporin antibiotics were more active against *S. paratyphi* A

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†† Send reprint requests to: Publications Editor, U.S. Naval Medical Research Unit No. 3, FPO New York, NY 09527.

TABLE 1. *Susceptibility of 67 strains of S. typhi to five cephalosporin antibiotics*

Antibiotic	Cumulative % of strains inhibited at various concn (μg/ml)						
	0.19	0.39	0.78	1.56	3.12	6.25	12.5
Cefamandole	69	92	98	98	100	100	100
Cefaclor	0	55	97	100	100	100	100
Cefazolin	0	0	52	97	100	100	100
Cephalothin	0	3	48	89	97	98	100
Cephalexin	0	0	0	0	73	100	100

TABLE 2. *Susceptibility of 54 strains of S. parathyphi A to five cephalosporin antibiotics*

Antibiotic	Cumulative % of organisms inhibited at various concn (μg/ml)							
	0.19	0.39	0.78	1.56	3.12	6.25	12.5	25
Cefamandole	0	9	35	94	100	100	100	100
Cefaclor	0	0	9	87	100	100	100	100
Cefazolin	0	0	0	39	100	100	100	100
Cephalothin	0	0	0	7	22	94	96	100
Cephalexin	0	0	0	0	0	31	98	100

than cephalothin or cephalexin (Table 2). The bactericidal activities of cefamandole and cefaclor were comparable, but cefazolin was slightly less potent than the other two. The 1.56-μg/ml concentration of cefamandole, cefaclor, and cefazolin inhibited 94, 87, and 39% of the *S. paratyphi* A strains, respectively. The 3.12-μg/ml concentration of these drugs inhibited 100% of the strains, but the same concentration of cephalothin inhibited only 22% of the isolates, and this concentration of cephalexin failed to inhibit a single strain. One hundred percent inhibition required cephalothin and cephalexin concentrations of 25 μg/ml.

The results of this study confirm several previous reports which have suggested that cefazolin, cefamandole, and cefaclor were more potent than their predecessors against salmonellae (2, 6, 7). The MIC values of these drugs for strains of salmonellae isolated in Egypt are comparable to those reported from the United States and other countries (1, 2, 6, 7, 10, 14). The relatively low MIC values of these newer cephalosporins suggest they may be useful in the therapy of salmonellosis, but their value will also depend on their activity against antibiotic-resistant strains and their activity in vivo. Cefamandole appears to be active in vitro against chloramphenicol-resistant strains of *S. typhi*, and both cefamandole and cefazolin seem to possess therapeutic efficacy in enteric fever (10, 14). However, these observations are quite preliminary and additional studies are clearly needed.

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