Pharmacokinetics and Safety of Cefamandole in Newborn Infants

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Cefamandole, a new parenteral cephalosporin antibiotic, was administered to 23 newborn infants with pustular skin infection due to *Staphylococcus aureus* for an average duration of 7.5 days. All the patients improved clinically. Elevation of serum glutamic oxaloacetic transaminase and eosinophilia were observed in nine infants each transiently during treatment. There were no abnormalities of renal functions and Coombs' test results remained negative. The levels of cefamandole in serum after either intravenous or intramuscular administration were higher and the mean life was longer than those previously reported in older infants, children, and adults.

Cefamandole (CM), a new semisynthetic cephalosporin antibiotic is more active against *Enterobacteriaceae* and *Enterobacter* than currently available cephalosporin preparations (5, 10, 12, 13). The spectrum also includes ampicillin-resistant strains of *Haemophilus influenzae* and *Staphylococcus aureus* resistant to methicillin (11, 12, 14). Previous studies have demonstrated its efficacy and pharmacokinetics in older infants, children, and adults (1, 4, 9, 14). Because of its spectrum and ability to achieve therapeutic concentrations in cerebrospinal fluid (9, 16; C. Liu, D. Hinthorn, P. Gerjarusak, L. H. Baker, D. L. Dworzack, and J. Harms, Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 17th, New York, N.Y., Abstr. no. 1, 1977) this drug may have a potential role in the therapy of infection in newborns. We have studied the pharmacokinetics and safety of this drug in a group of newborn infants. To our knowledge, this has not been previously described.

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MATERIALS AND METHODS

A total of 23 full-term newborn infants (17 males and 6 females), ranging in age from 11 to 23 days (mean, 15.7 days), were admitted for pustular skin infections. The pustular fluid, showing gram-positive cocci in each case, grew out *S. aureus* which were susceptible to CM (mean zone size, 22.3 mm; range, 19 to 27 mm) as determined by the Kirby-Bauer technique, utilizing 30- μ g disks. Blood cultures were sterile in all. The infants were treated intramuscularly (i.m.) with 33 mg of CM per kg every 8 h, for 6 to 9 days

(mean, 7.5 days). Written informed consent was obtained from parents of all patients.

Each patient was examined daily for evidence of adverse clinical effects, and in addition, serum glutamic oxaloacetic transaminase (SGOT), bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine and urinalysis, complete blood count, and serial Coombs' test were determined before admission, midway through, and 1 to 2 days after the completion of therapy.

Pharmacokinetic studies. Pharmacokinetic studies were performed after the last dose, which varied as to the amount and route of administration in one of four ways: (i) 33 mg/kg i.m. (ii) 17 mg/kg i.m.; (iii) 33 mg/kg intravenously (i.v.); and (iv) 17 mg/kg i.v. The i.m. dose of CM at a concentration of 250 mg/ml was given in the anterolateral aspect of the thigh. The i.v. dose, prepared at a concentration of 25 mg/ml in 5% dextrose water, was infused in a peripheral vein over a 5-min interval. Serum for the determination of CM concentration was collected by heel prick just before the test dose, 0.25 h after i.v. dose, and 0.5, 1, 4, and 8 h after both i.m. and i.v. doses. The sera were kept frozen at -40°C before the determination of drug level, which was performed by an agar diffusion method utilizing *Bacillus subtilis* as the test organism (3).

Calculation of half-life and volume distribution. Serum antibiotic concentrations were plotted in a semilogarithmic manner against time. The serum half-life ($t_{1/2}$) was calculated when levels were declining exponentially during the elimination phase by the equation $t_{1/2} = \ln 2/K$, where K is the elimination rate constant, represented by the slope of the regression line determined by the method of least squares (8).

The volume of distribution ($V_d = (\text{dose [mg]} \times 1,000/E_c [\mu\text{g/ml}]) \times \text{weight [kg]}$), where E_c is the estimated serum concentration at the onset of the elimination phase, was obtained by extrapolating the serum concentration curve back to the y axis (7).

Three infants having antibiotic activity in the zero-hour serum specimen (before the test dose) were excluded from the evaluation of $t_{1/2}$ and V_d .

Statistical analyses were performed by using the Student's t test and the method of least squares.

RESULTS

Serum concentrations, half-life, and volume distribution of CM are presented in Table 1. In each dosage group, the serum concentrations obtained by the i.m. and i.v. routes were similar at the different times involved. However, the levels were about twice as high with the 33 mg/kg dose than with the 17 mg/kg dose ($P < 0.01$), regardless of route of administration. The mean half-life was approximately 1 h for both doses and routes of administration. The calculated mean volume of distribution was about equal for three of the four groups. However, in the 33 mg/kg i.v. group, it was significantly smaller ($P < 0.05$) than for the three other groups. The skin lesions in each case disappeared by day 5, and no untoward reactions, such as skin eruptions, diarrhea or vomiting, and swelling or abscess formation, were observed. Transient elevation of SGOT and eosinophilia (eosinophil count up to 7%) occurred in nine infants each, including two infants who developed both. The mean pre-therapy SGOT level ($56 \text{ U} \pm 23$ standard deviation) in these nine infants increased significantly to $84 \text{ U} (\pm 39; P < 0.05)$ during therapy; the level decreased to a mean $40 \text{ U} (\pm 28)$ after treatment. The Coombs' test remained negative in all, and the renal functions showed no abnormalities. Pre-, intra-, and post-therapy values for mean BUN were 10.3, 8.8, and 10.7 mg/dl, respectively, and for mean serum creatinine were 0.7, 0.6, and 0.7 mg/dl, respectively.

DISCUSSION

The serum levels observed in this study were in general considerably higher than the minimal

inhibitory concentrations (MICs) against bacteria commonly associated with neonatal infection. We did not determine the MICs of CM against the organisms isolated in our study. Previous studies, however, have shown that the MIC of CM for 100% of the strains of *S. aureus* ranges from 0.5 to 8 $\mu\text{g/ml}$ (10), and for over two-thirds of strains of *E. coli* and *Klebsiella* it ranges from 0.5 to 1.0 $\mu\text{g/ml}$. The MICs of CM against *Proteus*, *Salmonella*, *Shigella*, and group B streptococcus are in similar ranges (10). Against *Listeria*, however, the MICs of CM are higher (4 to 8 $\mu\text{g/ml}$), and against *Enterococcus* they are still higher (16 to 32 $\mu\text{g/ml}$) (10). *Pseudomonas*, most of *Serratia* and *Acinetobacter*, and about 40% of *Enterobacter* strains, however, are not inhibited by CM (10). The latter organisms, however, are unusual pathogens during the newborn period.

The higher serum levels and longer half-life as compared with those observed in older infants and children may perhaps reflect a larger volume of distribution and/or a decreased glomerular filtration in newborn infants. The similarity in half-life between the i.m. and i.v. route observed in newborns, in contrast to older subjects whose i.m. $t_{1/2}$'s are longer than those with the i.v. route (4, 6), may likewise be due to immature renal functions and/or a larger volume of distribution. The smaller mean volume of distribution observed in the group receiving 33 mg/kg i.v. cannot be readily explained, but may be due specifically to the small sample size (only three subjects).

The clinical recovery observed with CM was not unexpected and can also be anticipated with other cephalosporins. The observed changes in eosinophil count and SGOT were similar to those reported by us in older children treated with CM (4). The elevated SGOT may have been at least in part due to i.m. administration.

Further studies are needed to determine the pharmacokinetics of CM in infants younger than

TABLE 1. Pharmacokinetics of CM after the last dose^a

Dose (mg/kg)	No. of cases	Mean serum concn ($\mu\text{g/ml}$)						Mean half-life (min)	Mean V_d (ml/kg)
		0 h	0.25 h	0.5 h	1 h	4 h	8 h		
33, i.m.	7	0.8 ^b		72 (46-127)	49.4 (20-140)	5.3 (1.2-18)	0.7 (0-3.4)	72.6 (51.0-98.0)	481.6 (235.0-990.0)
33, i.v.	5	0	106.0 (83-133)	83.6 (76-117)	64.0 (24-90)	5.7 (0-14.0)	0.5 (0-2.7)	56.0 (22.0-87.0)	260.0 (209.0-362.0)
17, i.m.	7	0.6 ^b		34.6 (18-53)	19.6 (14-32)	2.2 (1.4-3.8)	0.14 (0-0.5)	68.0 (41.0-116.0)	476.0 (262.0-664.0)
17, i.v.	4	1.06 ^b	50.5 (37-63)	42.0 (29-53)	26.3 (17-38)	1.8 (1.1-3.6)		61.0 (49.0-69.0)	415.0 (229.0-874.0)

^a Values in parentheses indicate range.

^b One case in each group was due to previous doses.

2 weeks and its ability to cross the blood-brain barrier in newborn infants. In the absence of information in this area, CM or any other cephalosporin antibiotic cannot be recommended for neonatants in whom systemic infection is suspected.

LITERATURE CITED

1. Azimi, P. H. 1978. Clinical and laboratory investigation of Cefamandole therapy of infections in infants and children. *J. Infect. Dis.* 137(Suppl.):S155-160.
2. Bauer, A. W., W. M. M. Kirby, J. C. Sherris, and M. Turck. 1966. Antibiotic susceptibility testing by a standardized disc method. *Am. J. Clin. Pathol.* 45:493-496.
3. Bennett, J. V., J. L. Brodie, E. J. Benner, and W. M. M. Kirby. 1966. Simplified, accurate method for antibiotic assay of clinical specimens. *Appl. Microbiol.* 14:170-177.
4. Chang, C. T., A. J. Khan, M. M. Agbayani, R. C. Jhaveri, I. Amin, and H. E. Evans. 1978. Pharmacokinetics and safety of cefamandole in infants and children. *Antimicrob. Agents Chemother.* 14:838-841.
5. Eykyn, S., C. Jenkins, A. King, and I. Philips. 1973. Antibacterial activity of cefamandole, a new cephalosporin antibiotic, compared with that of cephaloridine, cephalothin, and cephalixin. *Antimicrob. Agents Chemother.* 3:657-661.
6. Fong, I. W., E. D. Ralph, E. R. Engelking, and W. M. M. Kirby. 1976. Clinical pharmacology of cefamandole compared with cephalothin. *Antimicrob. Agents Chemother.* 9:65-69.
7. Giacoia, G. P., and R. Gorodisher. 1975. Pharmacologic principles in neonatal drug therapy. *Clin. Perinatol.* 2:125-138.
8. Goldstein, A., L. Aronow, and S. Kalman. 1968. Principles of drug action, the basis of pharmacology, p. 142-288. Harper & Row, Publishers, New York.
9. Korzeniowski, O. M., E. Carvalho, Jr., H. Rocha, and M. A. Sande. 1978. Evaluation of cefamandole therapy of patients with bacterial meningitis. *J. Infect. Dis.* 137(Suppl.):S169-179.
10. Lilly Research Laboratory. 1976. Cefamandole nafate, p. 90. *In* Clinical investigation manual. Lilly Research Laboratories, Indianapolis, Ind.
11. Meyers, B. R., and S. Z. Hirschman. 1978. Antibacterial activity of cefamandole in vitro. *J. Infect. Dis.* 137(Suppl.):S25-31.
12. Meyers, B. R., B. Leng, and S. Z. Hirschman. 1975. Cefamandole: antimicrobial activity in vitro of a new cephalosporin. *Antimicrob. Agents Chemother.* 8:737-741.
13. Neu, H. C. 1974. Cefamandole, a cephalosporin antibiotic with an unusually wide spectrum of activity. *Antimicrob. Agents Chemother.* 6:177-182.
14. Rodriguez, W. J., S. Ross, W. N. Khan, and R. Goldenberg. 1978. Clinical and laboratory evaluation of cefamandole in infants and children. *J. Infect. Dis.* 137(Suppl.):S150-154.
15. Steinberg, E. A., G. D. Overturf, J. Wilkins, L. J. Baraff, J. M. Streng, and J. M. Leedom. 1978. Failure of cefamandole in treatment of meningitis due to *Haemophilus influenzae* type B. *J. Infect. Dis.* 137(Suppl.):180-186.
16. Steinberg, E. A., G. Overturf, L. Baraff, and J. Wilkins. 1977. Penetration of cefamandole into spinal fluid. *Antimicrob. Agents Chemother.* 11:933-935.