Cefsulodin Sodium Therapy in Cystic Fibrosis Patients

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Cefsulodin sodium is a narrow-spectrum cephalosporin with marked in vitro activity against clinical isolates of *Pseudomonas aeruginosa*. We have studied the antibiotic in a clinical trial in 10 patients admitted to the Pediatric Ward of the University of Virginia Medical Center with cystic fibrosis and recurrent acute lower respiratory tract infections with *P. aeruginosa* isolated from their sputa. The patients received 500 to 1,500 mg of cefsulodin every 6 hours by intravenous infusion for 10 to 22 days. Mean peak drug levels in plasma after 500, 1,000, and 1,500 mg were 46, 71, and 90 μg/ml, respectively, and the mean minimal inhibitory concentration of all organisms was 7.5 μg/ml. Detectable levels of cefsulodin in sputa were found in approximately half of the random samples and ranged from 2 to 5 μg/ml. The clinical response was satisfactory in nine (90%) of the patients. One patient gained weight and had improved pulmonary function tests but showed no reduction in sputum production and no improvement in arterial blood gas values. In pulmonary function tests, four of five patients tested showed an average 43% increase in forced vital capacity after initiation of therapy and five of five had an average 51% increase in forced expired volume in 1 s. No adverse effects were observed.

Cystic fibrosis, a common hereditary disease affecting 1 in 2,000 live births among whites and 1 in 17,000 among blacks (6), is characterized by recurrent episodes of bronchopneumonia frequently due to *Pseudomonas aeruginosa* (10). Cefsulodin sodium, a new semisynthetic third generation cephalosporin, has a high degree of activity against *P. aeruginosa* but very limited activity against other gram-negative pathogens (13). It is reported to be four- to eightfold more active than carbenicillin against *P. aeruginosa* (11), presumably owing to its increased affinity for penicillin-binding protein 1b and relative stability to the cephalosporin-ases of *P. aeruginosa* (12).

As with other cephalosporins, the excretion of cefsulodin is primarily renal, with 40 to 70% of the administered dose recovered from the urine within 24 h (14). It has a half-life of 1.6 h after intravenous administration in patients with normal kidney function (8) and 6 to 13 h in patients with moderate and severe impairment of renal function (7). The purpose of this report is to document the safety and efficacy of cefsulodin sodium in the therapy of 10 patients with cystic fibrosis, acute pulmonary decompensation, and *P. aeruginosa* as the sole or predominant pathogen in their sputa.

(This study was presented in part at the 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Miami Beach, Fla., 4 to 6 October 1982 [I. Cabezudo, R. L. Thompson, S. H. Guenthner, and R. P. Wenzel, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 1982, abstr. no. 67, p. 77].)

MATERIALS AND METHODS

Ten patients with cystic fibrosis admitted to the Pediatric Ward of the University of Virginia Medical Center were included in a clinical trial of cefsulodin. Their ages ranged from 13 to 22 years (mean, 17.5), and they or their parents gave consent for participation on a treatment protocol approved by the university's Human Experimentation Com-

mittee. All 10 patients had an acute exacerbation of chronic lower respiratory tract infection, defined as a change in pulmonary status with shortness of breath, increases in cough and in sputum production, and malaise. *P. aeruginosa* was isolated from their sputa as the sole or predominant pathogen (1) before their admission to the study. No patient had a previous history of penicillin or cephalosporin hypersensitivity.

Patients were examined daily to monitor possible side effects and for clinical response by research team personnel and by the primary physician. A complete urinalysis was performed and blood for hematological and chemical profiles was drawn before treatment and on days 5 and 10 of therapy and days 1 and 7 or 10 posttreatment. Pulmonary function tests were performed at the discretion of the primary physician. Five patients had tests of forced vital capacity, and five had tests of forced expired volume in 1 s.

Therapy consisted of intravenous administration of cefsulodin (kindly supplied by Abbott Laboratories, North Chicago, Ill.) over a 30-min period in dosages of 500, 1,000 or 1,500 mg every 6 h for 10 to 22 days; one patient however, was discharged after only 9 days of therapy. Additional measures, including supplemental oxygen, humidification, and chest physical therapy, were given when requested by the primary physician.

Plasma was obtained 30 min before and immediately after cefsulodin infusion for determination of trough and peak levels, respectively. The assay was done by an agar diffusion method, using *P. aeruginosa* NCTC 10490 as the test organism (5). The lower limit of sensitivity was 2 μg/ml. Sputum samples were obtained for Gram stain and culture at the same time as blood samples in six patients (no. 5, 6, 7, 8, 9, and 10) on 10 occasions and on different days in the other four patients. Initial drug level determinations in these samples were measured after the addition of phosphate buffer (5). Susceptibilities were determined by the disk diffusion method of Bauer and co-workers (3), and MICs were determined by the broth dilution technique as described by Barry (2). Serotyping of the different strains was

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performed at Abbott Laboratories (4). All of the assays were done in triplicate.

Clinical response was considered to be satisfactory if there was improved breathing and diminution of sputum production observed by the patient, his or her physician, and the research team investigator.

RESULTS

In 9 of the 10 patients, the clinical response was considered to be satisfactory by both patient and primary physician, and no change was observed in 1 patient. No adverse clinical or chemical reactions to cefsulodin sodium were noted during the course of therapy. Tests of forced vital capacity and forced expired volume in 1 s performed before and after therapy showed a mean increase of 43% in forced vital capacity in four of five patients tested (no. 1, 2, 5, and 7) and a mean increase of 51% in forced expired volume in 1 s in five patients tested (no. 1, 2, 6, 7, and 8). Of these, patients 1 and 2 had received 500 mg of cefsulodin sodium every 6 h, and patients 5, 6, 7, and 8 had received 1,000 mg every 6 hours. One patient (no. 8) who appeared to improve clinically showed a 24% decrease in forced vital capacity after therapy. However, the forced expired volume in 1 s of the same patient showed a 15% increase for the same interval.

Peak plasma levels ranged from 31 to 139 μg/ml with mean levels of 46, 71, and 90 μg/ml, respectively, after 500-, 1,000-, and 1,500-mg doses (Fig. 1). Sputum levels ranged from 2 to 5 μg/ml in eight patients and 19 samples and were less than 2 μg/ml in seven patients and 18 samples. Two patients (no. 4 and 6) had levels <2 μg/ml in all their samples (Fig. 2). MICs ranged from 0.2 to 128 μg/ml (geometric mean, 7.5 μg/ml). Of 15 strains, 3 (20%) that required for inhibition an MIC of ≤16 μg/ml were resistant (≤15 mm disk zone diameter) by Kirby-Bauer disk diffusion methods with a 30-μg disk, whereas 9 of 10 strains (90%) that required for inhibition an MIC of ≥32 μg/ml were also resistant by the disk diffusion method, for an overall correlation of 84% between MIC and disk diffusion tests.

After therapy, 13 isolates from six patients required for inhibition an MIC of ≥32 μg/ml. Three patients had isolates which appeared to have developed resistance only after therapy. Patient 3 had *P. aeruginosa* type 5, patient 6 had *P. aeruginosa* type 6, and patient 8 had *P. aeruginosa* type 5. In all 10 cases, colonization of lower respiratory secretions persisted after therapy, a characteristic feature in patients with cystic fibrosis.
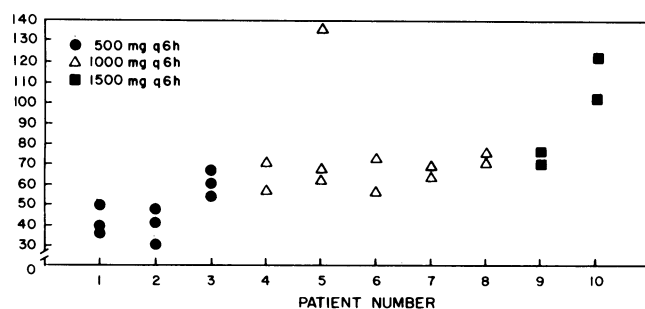

FIG. 1. Peak levels of cefsulodin sodium in plasma (in micrograms per milliliter) after intravenous administration of 500, 1,000, or 1,500 mg every 6 h.
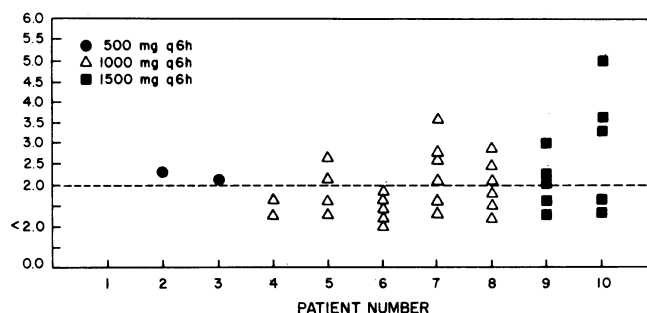

FIG. 2. Concentration levels of cefsulodin sodium in sputum (in micrograms per milliliter) after intravenous administration of 500, 1,000, or 1,500 mg every 6 h. Patients no. 4 and 6 had concentrations of less than 2 μg in all of their samples. The broken line indicates the lower limit of susceptibility.

DISCUSSION

Cefsulodin sodium has been generally well tolerated, and only occasionally have side effects such as nausea, dizziness, allergic skin reactions, and transient elevations of blood urea nitrogen, creatinine, and transaminases been reported. In the 10 patients we studied with cystic fibrosis, no clinical or chemical side effects were noted. The putative advantage in using cefsulodin sodium as a therapeutic agent in human *P. aeruginosa* infections is that current antibiotic regimens (an aminoglycoside plus an antipseudomonal penicillin) present the potential for relatively increased toxicity. Such toxicity is thought to be related to the narrow gap between therapeutic and toxic levels of aminoglycosides. In addition, there is the problem of the increased metabolism of aminoglycosides in cystic fibrosis patients, which requires a larger dose of the drug to achieve the therapeutic levels (9). On the other hand, it has been suggested that *P. aeruginosa* is able to develop a beta-lactamase membrane "barrier" that appears to be responsible for the resistance to beta-lactam antibiotics (15). This mechanism could have been involved in the three patients who had resistant *P. aeruginosa* isolates only after therapy.

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