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Randomized Double-Blind Evaluation of Ceftazidime Dose Ranging in Hospitalized Patients with Cystic Fibrosis

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Eighty-five patients with cystic fibrosis who were experiencing an acute infectious exacerbation of their disease were randomized in double-blind fashion to receive either 50 or 75 mg of ceftazidime per kg (body weight) per dose administered intravenously every 8 h for 14 days. Three patients were dropped from the study within 4 days of enrollment for reasons unrelated to drug administration. The total daily dose of ceftazidime administered was restricted by protocol design and was independent of the body weight of the patient. Thus, for datum analysis, patients were separated into three ceftazidime dosage groups (denoted as range of milligrams per kilogram per dose): group 1, 22 to 44.5; group 2, 46.3 to 56.6; and group 3, 66.7 to 80.6. Ceftazidime monotherapy had no effect on sputum colony counts for any *Pseudomonas cepacia* isolate. In contrast, a substantial reduction in *Pseudomonas aeruginosa* sputum colony counts was observed, and from 19 to 31% of isolates were suppressed $\geq 10^5$ CFU/ml after 14 days of therapy. Bacterial resistance in vitro was not observed, although a trend for increasing ceftazidime MICs was observed for group 1 patients ($P < 0.05$). Overall, clinical response appeared independent of drug dose, and no relationship could be identified between the reduction in *P. aeruginosa* sputum colony counts and clinical outcome. Adverse effects of ceftazidime were mild and transient, necessitating drug discontinuation in one patient. These data suggest that the clinical response to ceftazidime in patients with cystic fibrosis may be maximal with 50 mg/kg per dose (150 mg/kg per day) up to a total daily dose of 6 g.

Ceftazidime, an aminothiazolyl expanded-spectrum cephalosporin, demonstrates potent in vitro activity against *Pseudomonas aeruginosa* and *Pseudomonas cepacia* sputum isolates obtained from patients with cystic fibrosis (CF) (1, 7). Pharmacologic evaluations of ceftazidime in these patients have demonstrated altered biodisposition characteristics (8) similar to those observed for other antimicrobial agents in patients with CF (9, 12, 16). Our previous experience assessing the sputum penetration characteristics of ceftazidime in patients with CF revealed sputum drug concentrations which equalled or only marginally exceeded the MIC for pseudomonal isolates (2). Despite these potential pharmacologic limitations, numerous studies have documented the clinical efficacy of ceftazidime monotherapy in the treatment of acute pulmonary exacerbations experienced by patients with CF (2, 3, 6, 11). These data combined suggest that an increased total daily dose of ceftazidime might improve bacteriologic or patient clinical response. To evaluate this hypothesis, we undertook a randomized double-blind evaluation of the efficacy and tolerability of ceftazidime monotherapy administered in varying dosages to patients with CF who were experiencing an acute pulmonary exacerbation of their disease.

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MATERIALS AND METHODS

Patients ≧5 years of age with CF who were being monitored by the CF center at Rainbow Babies and Children's Hospital and who required hospitalization for acute pulmonary deterioration and parenteral antibiotic therapy were eligible for enrollment. A clinical diagnosis of acute pulmonary deterioration was made by the pulmonologist responsible for the patient when four or more of the following symptoms were present: (i) increasing productive cough, (ii) change in volume, appearance, or color of sputum, (iii) increased respiratory rate or dyspnea, (iv) progressive physical findings on chest auscultation, (v) new infiltrate on chest X ray, (vi) deterioration in pulmonary function revealed by pulmonary function testing, (vii) decreased appetite or weight loss, or (viii) fever. Patients were excluded from this study if they had a history of allergy to β-lactam antibiotics, liver functional impairment (serum bilirubin, ≧3 mg/dl; serum glutamic pyruvate transaminase, >100 IU/liter), renal functional impairment (serum creatinine, >1.5 mg/dl), or cor pulmonale requiring diuretic therapy or digoxin, or if the predominant sputum pathogen(s) isolated was resistant to ceftazidime. These studies were approved by the Institutional Review Board of the University Hospitals of Cleveland, and written informed consent was obtained from each family or patient. No patient received any additional oral, parenteral, or aerosolized antibiotic while receiving ceftazidime.

Conduct of the study. To be eligible for evaluation of clinical efficacy, ceftazidime monotherapy had to be received for a total of 14 days. Before enrollment and drug

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TABLE 1. Patient characteristics[a]

Characteristic	Ceftazidime dosage group		
	1	2	3
No. of patients (male/female)	9/6	20/8	23/16
Age (yr)	23 ± 6.7 (15–38)	18 ± 8.3 (7–42)	18 ± 6.4 (5–33)
Wt (kg)	56 ± 11.9 (45–89)	37 ± 14.4 (18–71)	39.3 ± 11.2 (14–61)
Serum creatinine (mg/dl)	0.9 ± 0.2 (0.6–1.2)	0.7 ± 0.1 (0.6–1.0)	0.7 ± 0.2 (0.3–1.2)
SGPT[b] (IU/liter)	29 ± 27 (8–114)	22 ± 18 (4–114)	22 ± 16 (3–170)
Albumin (g/dl)	3.7 ± 0.6 (2.7–4.6)	3.7 ± 0.5 (2.3–4.4)	3.6 ± 0.5 (2.5–4.5)
$PaCO_2$[c] (mm Hg)	37 ± 5 (32–49)	41 ± 7 (34–56)	41 ± 10 (29–72)
ACE score[d] (admission)	53 ± 12 (33–74)	47 ± 18 (20–83)	48 ± 19 (13–81)
Shwachman score[e] (admission)	57 ± 11 (39–78)	48 ± 10 (34–65)	53 ± 13 (25–83)

[a] See text for description of patient groups. Values are expressed as means ± standard deviation (range).
[b] SGPT, Serum glutamic pyruvic transaminase.
[c] Arterial carbon dioxide tension.
[d] Acute clinical efficacy score (2).
[e] Reference 13.

administration, each child underwent a complete physical examination and laboratory evaluation which included serum electrolytes, tests of liver and renal function, a complete blood count with differential and platelet count, microscopic and macroscopic urinalysis, arterial blood gas, pulmonary function testing, chest X ray, and sputum culture. Patients were examined daily, and laboratory evaluation was performed upon initiation of therapy and on days 7 and 14 of therapy.

Dosage randomization. Patients were randomized to receive one of two doses of ceftazidime stratified according to body weight. Patients received either 50 mg of ceftazidime per kg per dose up to a maximum single dose of 2 g or 75 mg of ceftazidime per kg per dose up to a maximum single dose of 4 g. Thus, the maximum allowable ceftazidime dose was restricted by protocol design independent of the body weight of a patient, i.e., 6 g of ceftazidime per day for patients randomized to receive 150 mg of ceftazidime per kg per day (50 mg/kg per dose) and 12 g of ceftazidime per day for those patients randomized to receive 225 mg of ceftazidime per kg per day (75 mg/kg per dose). Each drug dose was administered intravenously over 10 to 20 min every 8 h. Study investigators and patients were blinded to the actual ceftazidime dose administered until completion of the study. Randomization, drug blinding, and dose preparation was performed by the professional staff of the Department of Pharmacy Services.

Bacteriology. Qualitative and quantitative sputum cultures were obtained before ceftazidime administration and again on days 7 and 14 of therapy. Sputum was collected by expectoration into sterile cups or, from younger children, by nasotracheal aspiration into a sterile specimen trap. For qualitative evaluation, the sputum was plated on 5% sheep blood, chocolate, and MacConkey agars. For quantitative evaluation, 0.5 ml of sputum was diluted with 50 ml of sterile phosphate-buffered saline (pH 7.2) and homogenized by using a Brinkman Polytron Homogenizer. Serial 10-fold dilutions from 10^{-3} to 10^{-9} were spread on tryptic soy, 5% sheep blood, chocolate, and MacConkey agars with glass rods for quantitative counting. Determination of MICs of ceftazidime, piperacillin, and tobramycin for all isolates was performed by standard agar dilution techniques.

Clinical efficacy. The clinical course of each patient and his or her response to therapy was determined clinically by the patient's pulmonologist (i.e., good improvement, fair improvement, or treatment failure), and at days 0, 7, and 14 by an acute clinical efficacy scoring system (2). This acute scoring system assigns a maximum of 100 points for critical evaluations in eight categories including sputum volume (0 to 5 points), peak body temperature (0 to 5 points), sleeping respiratory rate (1 to 5 points), change in body weight (0 to 4 points), chest physical exam (0 to 36 points), arterial blood gas determination (0 to 10 points), pulmonary function testing (0 to 20 points), and exercise tolerance (0 to 15 points). All scoring was performed by one trained observer. In addition, on days 0 and 14 of therapy, each patient was evaluated by the scoring system of Shwachman and Kulczycki (13).

Statistical evaluation. Analysis of variance was used to determine whether differences existed between patient study groups, and the paired and unpaired Student's t test was used to assess for differences within an individual patient study group.

RESULTS

A total of 85 patients were enrolled in this study. Three patients were dropped from the study within 4 days of enrollment; two were dropped because of the isolation of ceftazidime-resistant sputum isolates, and one died within 24 h of hospital admission with aplastic anemia diagnosed on admission unrelated to drug administration. Because of the protocol restrictions on the total daily ceftazidime dose, larger patients (by body weight) received less drug on a milligram-per-kilogram basis than anticipated. As a result, ceftazidime dosage appeared to conform to a trimodal distribution. To accurately define these three patient groups, a trimodal distribution model with equal variances was fitted to ceftazidime dose, and maximum likelihood estimates were obtained by using MAXLIK (5). Two distinct separation values were determined, minimizing the possibility of misclassification between two adjacent distributions. Thus, for datum analysis, study patients were separated into three different ceftazidime dosage groups [dosage, in milligrams of ceftazidime per kilogram per dose, is expressed as the mean ± standard deviation (range)]: group 1, 37 ± 6.4 (22 to 44.5); group 2, 51 ± 2.7 (46.3 to 56.6); and group 3, 74 ± 2.5 (66.7 to 80.6). The potential for misclassification of a true trimodal distribution for the three patient groups is 7.3%.

Characteristics for the 82 evaluable patients subdivided by ceftazidime dose are shown in Table 1. Only slight differences in patient age, admission clinical scores, and biochemical laboratory determinations were observed between patients in the three study groups. Most study patients had

TABLE 2. Comparative in vitro susceptibility of sputum isolates obtained on hospital admission

Organism (no. of isolates)	MIC (μg/ml)[a]					
	Ceftazidime		Piperacillin		Tobramycin	
	50%	90%	50%	90%	50%	90%
Group 1						
P aeruginosa (16)	8	32	64	256	>8	>8
P. cepacia (7)	1	2	8	16	>8	>8
Group 2						
P. aeruginosa (34)	16	>64	128	>256	4	>8
P. cepacia (16)	1	4	32	128	>8	>8
Group 3						
P. aeruginosa (42)	8	>64	64	>258	4	>8
P. cepacia (18)	1	4	8	64	>8	>8

[a] 50% and 90%, MIC for 50 and 90% of the isolates, respectively.

TABLE 4. Comparison of pre- and posttherapy in vitro activity of ceftazidime against sputum isolates

Organism	Pretherapy			Posttherapy		
	No. of isolates	MIC (μg/ml)[a]		No. of isolates	MIC (μg/ml)[a]	
		50%	90%		50%	90%
Group 1						
P. aeruginosa[b]	16	8	32	13	32	64
P. cepacia	7	1	2	7	2	8
Group 2						
P. aeruginosa	34	16	>64	27	16	>64
P. cepacia	16	1	4	16	1	8
Group 3						
P. aeruginosa	42	8	>64	29	16	>64
P. cepacia	18	1	4	18	2	8

[a] 50% and 90%, MIC for 50 and 90% of the isolates, respectively.
[b] The difference between pretherapy and postherapy ceftazidime MICs was statistically significant ($P < 0.05$).

severe disease as reflected by their admission clinical scores. Because of dosing restrictions, patients in group 1 were heavier than group 2 and 3 patients.

Bacteriologic response. A total of 92 different morphotypes of *P. aeruginosa* and 41 *P. cepacia* isolates were obtained and identified on admission in sputum culture. Sputum colony counts ranged from 10^5 to 10^9 CFU/ml for *P. aeruginosa* and 10^6 to 10^9 CFU/ml for *P. cepacia*. In group 1, 7 patients had *P. aeruginosa* and 3 patients had *P. cepacia* as their sole sputum isolates; in group 2, 10 patients had *P. aeruginosa* and 5 patients had *P. cepacia*; and in group 3, 21 patients had *P. aeruginosa* and 14 patients had *P. cepacia*. The distribution of these isolates by study group and by their in vitro susceptibility to ceftazidime, piperacillin, and tobramycin is shown in Table 2. Ceftazidime demonstrated the greatest degree of in vitro activity. Most *P. aeruginosa* and all *P. cepacia* isolates were resistant in vitro to tobramycin. Piperacillin demonstrated a greater degree of in vitro activity against *P. cepacia* than against *P. aeruginosa*, although overall it demonstrated only a moderate degree of in vitro activity.

Ceftazidime monotherapy had no effect on sputum colony counts of any *P. cepacia* isolate. In contrast, ceftazidime monotherapy resulted in a substantial reduction in *P. aeruginosa* sputum colony counts (Table 3). *P. aeruginosa* isolates in groups 1, 2, and 3 showed a $\geq 10^3$ CFU/ml reduction in sputum colony count in 44, 44, and 50% of isolates, respectively. Of these *P. aeruginosa* isolates, 19, 21, and 31%, respectively, were suppressed by $\geq 10^5$ CFU/ml at the end of therapy for the three groups.

Comparison of pre- and posttherapy in vitro activity of ceftazidime for *P. aeruginosa* and *P. cepacia* is shown in Table 4. Changes in the MICs for 50 and 90% of the isolates obtained from group 2 and group 3 patients were slight, varying one tube dilution at most, and were statistically insignificant. A fourfold increase was observed in the ceftazidime MIC for *P. aeruginosa* sputum isolates obtained from group 1 patients, and this increase was statistically significant ($P < 0.05$).

TABLE 3. Effect of ceftazidime monotherapy on *P. aeruginosa* sputum colony counts

Reduction (CFU/ml of sputum) from pretherapy sputum cultures	No. (%) of isolates showing the indicated reduction in:		
	Group 1 ($n = 16$)[a]	Group 2 ($n = 34$)[a]	Group 3 ($n = 42$)[a]
10^3–$<10^4$	3 (19)	4 (12)	2 (5)
10^4–$<10^5$	1 (6)	4 (12)	6 (14)
$\geq 10^5$	3 (19)	7 (21)	13 (31)
Total $\geq 10^3$	7 (44)	15 (44)	21 (50)

[a] Total number of *P. aeruginosa* isolates on pretherapy sputum culture.

Clinical efficacy of ceftazidime monotherapy. Clinical response of a patient to ceftazidime monotherapy was assessed independently by the patient's pulmonologist on a subjective basis and by one of the investigators on an objective basis by using the acute clinical efficacy scoring system. All evaluators, clinicians, and patients were blinded to the ceftazidime dosage being administered. The median scores for group 1, 2, and 3 patients pretherapy were 53, 45, and 49, respectively, which increased to 72, 62, and 67 upon completion of therapy. The prestudy means in acute clinical scores for the three groups were 53, 47, and 48, respectively, which increased to 70, 61, and 72 posttherapy. The prestudy mean Shwachman scores for the three groups were 57, 48, and 53, respectively, increasing to 62, 51, and 57 posttherapy. The observed improvement in both acute clinical efficacy score and Shwachman score for each of the three study groups was statistically highly significant ($P < 0.001$). However, no statistical differences were observed for changes in elinical scores between the three different groups. The observed changes and improvement in clinical scores appeared independent of the ceftazidime dose administered, as well as of initial sputum microbiology and magnitude of reduction in *P. aeruginosa* sputum colony counts. No correlation between ceftazidime dosage and clinical outcome or extent of reduction of bacterial counts in sputum of patients whose sputum yielded only *P. aeruginosa* could be identified. In the clinical assessment by the pulmonologist, all group 1 patients, 25 group 2 patients, and 31 group 3 patients were considered to have shown good clinical improvement. One group 3 patient was considered to have failed ceftazidime monotherapy.

Safety of ceftazidime monotherapy. Overall, ceftazidime was well tolerated by all patients. Adverse effects associated with ceftazidime therapy appeared independent of the dose administered. One group 1 patient complained of intermittent headaches, and one each in groups 2 and 3 complained of intermittent nausea after drug administration. Four pa-

tients (three in group 3) developed asymptomatic increases in serum glutamic pyruvic transaminase, and one patient each in groups 2 and 3 developed a peripheral eosinophilia (>650/mm^3). All of these clinical and laboratory effects were transient in nature and required no therapeutic intervention. Two group 2 patients developed a mild pruritic skin rash which responded to oral diphenhydramine. One group 3 patient developed hematuria on day 10 of therapy which persisted for 2 days, at which time drug therapy was discontinued. The hematuria resolved within 24 h and was not associated with any change in serum creatinine, blood urea nitrogen, or urine output.

DISCUSSION

The biodisposition of many antibiotics, including ceftazidime, has been shown to be different in patients with CF as compared with individuals without CF (8, 9, 12, 16). In general, patients with CF display a larger volume of distribution and eliminate these agents from the body more rapidly than patients without CF. These two pharmacokinetic characteristics combined support the frequent need for increased drug doses for certain agents in patients with CF. However, empirically increasing the daily dose of an antibiotic in these children may not be directly associated with an improved bacteriologic or clinical response and may subject patients to an unacceptable risk of untoward reactions.

In a randomized double-blind fashion, we assessed the effect of different doses of ceftazidime on sputum microbiology and clinical response in acutely ill patients with CF. Although the study was initially designed to assess two different ceftazidime dosage regimens (i.e., 50 versus 75 mg/kg per dose administered every 8 h), protocol restrictions, independent of body weight, on the maximum allowable dose stratified patients into three dose groups. Group 1 patients received a mean ceftazidime dose of 37 mg/kg, group 2 patients received a mean dose of 51 mg/kg, and group 3 patients received a mean dose of 74 mg/kg. Each dose was administered three times daily every 8 h.

Overall, changes observed in sputum microbiology, clinical efficacy, and the occurrence of drug-associated reactions appeared independent of drug dose. The magnitudes of reduction in sputum colony counts of *P. aeruginosa* isolates at the end of therapy were similar for the three patient groups. In contrast, ceftazidime monotherapy had no effect on sputum colony counts for any *P. cepacia* isolate. The absence of an effect on *P. cepacia* sputum isolates was observed despite the potent activity ceftazidime demonstrated in vitro against this microorganism (Table 2) relative to achievable ceftazidime concentrations in sputum reported previously (2, 11). Moreover, a dramatic effect on sputum *P. aeruginosa* colonization was observed, even though ceftazidime displayed less potency and variable in vitro activity against these isolates. The reason for these discrepancies is unclear, although previous work at our center and elsewhere has described similar findings (2, 4). These data reaffirm that not all patients with CF who are colonized with *P. cepacia* experience an accelerated deterioration in their clinical status which is frequently unresponsive to therapeutic intervention (4, 15).

A larger proportion of group 3 patients (14 of 39) than of group 1 and 2 patients had *P. cepacia* as their sole sputum isolate. Considering the failure of ceftazidime to affect sputum colony counts of *P. cepacia*, it is possible that this random occurrence blunted the clinical response experienced by group 3 patients. However, this is unlikely as we were unable to identify any difference in clinical outcome for patients who had only *P. cepacia*, only *P. aeruginosa*, or combined *P. cepacia* and *P. aeruginosa* sputum isolates. These observations are consistent with the recent experience of Gold and colleagues in Toronto (3). Furthermore, and as reported by others, we were unable to identify any relationship between clinical response and the observed reduction in sputum colony counts for *P. aeruginosa* (3, 10, 14).

The incidence of ceftazidime-associated adverse effects in our patients was low and consistent with previously reported experiences (2, 3, 6, 11). In all but one patient, drug-associated clinical effects and alterations in laboratory determinations were transient and resolved without the need to discontinue therapy.

Higher-dose therapy, as compared with recommended and lower-dose ceftazidime therapy, did not result in an appreciable difference in the clinical outcome of acutely ill patients with CF. Although group 1 patients improved as much as group 2 and group 3 patients, lower-dose therapy may be associated with an increased development of sputum isolate resistance to ceftazidime. However, the statistically significant difference ($P < 0.05$) observed in the ceftazidime MIC for *P. aeruginosa* sputum isolates obtained from group 1 patients should be interpreted with caution. Considering the increase in ceftazidime MIC relative to the in vitro susceptibilities of initial isolates, further study is needed to more accurately describe any relationship that may exist between ceftazidime dose, monotherapy, and in vitro susceptibility of isolates. Thus, on clinical grounds, the current dosing recommendation of 150 mg/kg per day up to 6 g appears adequate.

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