ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1996, p. 691–695 Vol. 40, No. 3
0066-4804/96/$04.00+0

Continuous Infusion versus Intermittent Administration of Ceftazidime in Critically Ill Patients with Suspected Gram-Negative Infections

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Received 3 July 1995/Returned for modification 27 October 1995/Accepted 21 December 1995

The pharmacodynamics and pharmacokinetics of ceftazidime administered by continuous infusion and intermittent bolus over a 4-day period were compared. We conducted a prospective, randomized, crossover study of 12 critically ill patients with suspected gram-negative infections. The patients were randomized to receive ceftazidime either as a 2-g intravenous (i.v.) loading dose followed by a 3-g continuous infusion (CI) over 24 h or as 2 g i.v. every 8 h (q8h), each for 2 days. After 2 days, the patients were crossed over and received the opposite regimen. Each regimen also included tobramycin (4 to 7 mg/kg of body weight, given i.v. q24h). Eighteen blood samples were drawn on study days 2 and 4 to evaluate the pharmacokinetics of ceftazidime and its pharmacodynamics against a clinical isolate of *Pseudomonas aeruginosa* (R288). The patient demographics (means ± standard deviations) were as follows: age, 57 ± 12 years; sex, nine males and three females; APACHE II score, 15 ± 3; diagnosis, 9 of 12 patients with pneumonia. The mean pharmacokinetic parameters for ceftazidime given as an intermittent bolus (IB) (means ± standard deviations) were as follows: maximum concentration of drug in serum, 124.4 ± 52.6 μg/ml; minimum concentration in serum, 25.0 ± 17.5 μg/ml; elimination constant, 0.268 ± 0.205 h^{-1}; half-life, 3.48 ± 1.61 h; and volume of distribution, 18.9 ± 9.0 liters. The steady-state ceftazidime concentration for CI was 29.7 ± 17.4 μg/ml, which was not significantly different from the targeted concentrations. The range of mean steady-state ceftazidime concentrations for the 12 patients was 10.6 to 62.4 μg/ml. Tobramycin peak concentrations ranged between 7 and 20 μg/ml. As expected, the area under the curve for the 2-g q8h regimen was larger than that for CI ($P = 0.003$). For IB and CI, the times that the serum drug concentration was greater than the MIC were 92 and 100%, respectively, for each regimen against the *P. aeruginosa* clinical isolate. The 24-h bactericidal titers in serum, at which the tobramycin concentrations were <1.0 μg/ml in all patients, were the same for CI and IB (1:4). In the presence of tobramycin, the area under the bactericidal titer-time curve (AUBC) was significantly greater for IB than CI ($P = 0.001$). After tobramycin was removed from the serum, no significant difference existed between the AUBCs for CI and IB. We conclude that CI of ceftazidime utilizing one-half the IB daily dose was equivalent to the IB treatment as judged by pharmacodynamic analysis of critically ill patients with suspected gram-negative infections. No evaluation comparing the clinical efficacies of these two dosage regimens was performed.

The most effective mode of administration of parenteral β-lactam antibiotics for the treatment of bacterial infections remains controversial. Clinically, β-lactams are commonly administered by intermittent infusions. In the past decade, continuous infusion has been advocated as an alternative method of administration on the basis of both the pharmacodynamic and the pharmacokinetic properties of these antibiotics. Unlike aminoglycosides, which exhibit concentration-dependent killing, the β-lactams demonstrate concentration-independent killing, achieving maximal killing at concentrations of four or five times the MIC for the organism (7, 10, 11, 35). The extent of bactericidal activity appears to depend more on the time that concentrations in serum are above the MIC (T>MIC) than on the magnitude of antibiotic concentrations (11, 14, 16, 21, 33). Additionally, virtually no β-lactams possess an appreciable postantibiotic effect against gram-negative bacilli (4, 5). Intermittent administration produces high peak and low trough concentrations in serum which may fall below the MIC for the organism during the dosing interval. Continuous intravenous (i.v.) administration produces a relatively consistent concentration of antibiotic that can be maintained above the MIC, thereby optimizing the pharmacodynamic properties of the β-lactams.

A recent study of continuous-infusion ceftazidime conducted with healthy volunteers found that serum bactericidal titers (SBTs) of ≥1:2 and a T>MIC of 100% can be achieved with 2- or 3-g continuous infusions of ceftazidime (27). Published case reports (12, 13, 17) and older clinical trials (3, 18) also demonstrated the effectiveness of continuous infusion in patients. The objectives of this study were (i) to compare the pharmacokinetic and pharmacodynamic parameters of ceftazidime administered by continuous infusion and intermittent bolus in critically ill patients, (ii) to determine the ability to achieve a targeted serum ceftazidime concentration of 20 ± 5 μg/ml by using a 3-g continuous infusion in critically ill patients (calculations were based on average pharmacokinetic parameters for ceftazidime), and (iii) to evaluate the relationship

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between ceftazidime clearance and estimated creatinine clearance.

MATERIALS AND METHODS

Patients. Patients who were admitted to the Medical Intensive Care Unit of Detroit Receiving Hospital between November 1994 and April 1995 and who met the following criteria were eligible for enrollment in the study: (i) suspected gram-negative bacteremia or pneumonia (bacteremia was defined as at least one positive blood culture with a gram-negative organism; pneumonia included at least two of the following: leukocyte count of $>10{,}000/mm^3$, new infiltrate on a chest radiograph, a maximum temperature of >101°F [ca. 38.3°C], a sputum smear showing >25 polymorphonuclear leukocytes and <10 epithelial cells per field and a predominance of gram-negative organisms, and a requirement of an increase in FiO_2 (fraction inspired oxygen) of >0.2 or an inability to be weaned from mechanical respiratory support), (ii) susceptibility of any pathogenic gram-negative isolates to ceftazidime and tobramycin, (iii) age of 18 years or more, and (iv) treatment of infection expected to continue for more than 4 days. Patients were excluded if they had documented hypersensitivity to cephalosporins or aminoglycosides or an estimated creatinine clearance of <40 ml/min or were in circulatory shock (which was defined as a systolic blood pressure of <90 mm Hg). Initial patient demographic data (age, weight, diagnosis, and APACHE II score) were collected upon enrollment in the study. Data collection included maximum daily temperature, leukocyte count, serum urea nitrogen and creatinine, and 24-h urine collection while the patient was enrolled in the study. Patients with a change in estimated creatinine clearance of >20 ml/min during the study period were not included in the final evaluation. This study was approved by the Wayne State University Human Investigations Committee, and informed consent was obtained for all patients prior to study participation.

Study design. This was a prospective, randomized, crossover trial. Patients were randomized to receive ceftazidime either as a 2-g i.v. loading dose followed by a 3-g continuous infusion over 24 h or as a 2-g bolus administered intermittently i.v. every 8 h (q8h), each for 2 days. The patients were then crossed over and received the opposite regimen for 2 days. Each regimen also included tobramycin (4 to 7 mg/kg of body weight, given i.v. q24h). The tobramycin was dosed to achieve a targeted concentration in serum for each patient. The targeted concentrations were dependent upon the site of the infection (22). Tobramycin peak and 8-h levels were also determined on the second and fourth days of the study. If necessary, tobramycin doses were adjusted by one of the investigators. Steady-state ceftazidime concentrations were expected to be achieved by days 2 and 4 of the study, at which time pharmacokinetic and pharmacodynamic analyses were performed.

Antimicrobial agent administration. All patients enrolled in the study received ceftazidime (Fortaz; Glaxo Pharmaceuticals, Research Triangle Park, N.C.). For the continuous infusions, the drug was reconstituted according to the manufacturer's guidelines and then further diluted in 100 ml of dextrose (5% in water) prior to i.v. administration. The intermittent-bolus doses were obtained from the manufacturer as premixed doses containing 2 g of ceftazidime in 50 ml of 5% dextrose in water. Tobramycin was diluted in 50 ml of 5% dextrose in water. All ceftazidime continuous infusions were administered via an infusion pump (Smith-Nephew Sigma, Inc., Medina, N.Y.) over 24 h. The i.v. bolus infusions of both ceftazidime and tobramycin were given over a period of 30 min, also via an infusion pump.

Blood sampling. Blood samples (3 ml) for ceftazidime pharmacokinetic and pharmacodynamic analyses were obtained prior to the start of dosing on days 2 and 4, at 0, 1.5, 4, 6, 8, 9, 16, 17, and 24 h after the start of the infusion. An additional 3-ml sample of blood was drawn at 1.5 and 8 h for serum tobramycin concentration assay. All blood samples were drawn from indwelling arterial catheters. The blood samples were allowed to clot at room temperature for 15 min. Following centrifugation (4,500 × *g* for 15 min at 25°C), the serum was divided into two portions, one for ceftazidime concentration determination and the other for bactericidal activity testing. All serum samples were stored at −25°C until the time of analysis.

Urine collection. Twenty-four-hour urine collection was performed on days 2 and 4 for each patient enrolled in the study. The urine volume was measured, and a small aliquot was obtained from the total volume and stored at −25°C until analysis. Urine creatinine was determined by the institution's clinical chemistry laboratory. Twenty-four-hour creatinine clearance was calculated by standard methods (34, 34a). Estimated creatinine clearance was calculated by the previously described method of Cockroft and Gault (9).

Test organism. The organism chosen for the SBT determination was *Pseudomonas aeruginosa* R288, which was obtained from the first patient enrolled in the study. The MIC and MBC of ceftazidime and tobramycin for this isolate were determined by the microdilution technique according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines (25). Ceftazidime pentahydrate (lot 130634; Glaxo Pharmaceuticals) and tobramycin sulfate (lot 44H04451; Sigma) were utilized.

Serum bactericidal activity. SBTs were determined two to four times for each subject for both antibiotic regimens in the presence and absence of tobramycin. Cation-supplemented Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) was utilized for dilution of patient serum according to NCCLS guidelines (26). The area under the bactericidal titer-time curve (AUBC) was calculated by the trapezoidal rule using the reciprocal of the SBT from 0 to 24 h for each regimen both with and without tobramycin (2). The tobramycin was eliminated from the serum samples by the addition of approximately 50 mg of cellulose phosphate (lot 125F0252; Sigma), which binds the aminoglycoside. The samples were vortexed periodically over 10 min and then centrifuged at 4,500 × *g* for 10 min, and the supernatant was removed for testing. Various supernatant samples were reassayed for ceftazidime concentration to verify that the cellulose phosphate did not interfere with the ceftazidime bactericidal activity. In addition, serum samples were reassayed for tobramycin concentration after the addition of the binding resin to verify the removal of tobramycin.

Analytical methods. Ceftazidime concentrations in serum were determined by using modified high-pressure liquid chromatography (HPLC) (20). The limit of detection was 2.5 μg/ml. Standards between 10 and 160 μg/ml were used to calibrate the assay (correlation coefficient, 0.999). The interday coefficient of variation for the 110-μg/ml control was 3.5%, and that for the 30-μg/ml control was 6.5%. Tobramycin concentrations were determined by fluorescence polarization immunoassay (TDx; Abbott Laboratories, Irving, Tex.) by the clinical toxicology laboratory at Detroit Receiving Hospital.

Pharmacokinetic analysis. Data for serum ceftazidime concentrations were fit via polyexponential functions with a nonlinear least-squares regression program (R-Strip, version 3.1; MicroMath Inc., Salt Lake City, Utah). The minimum number of exponentials needed to describe the curve was determined with a modified Akaike Information Criteria test with a weighted factor of $1/y^2$. The area under the concentration-time curve (AUC) over the dosing interval was calculated by trapezoidal rule with the LAGRAN program, version 2.1 (28). The steady-state volume of distribution was calculated by using the formula of Gibaldi and Perrier (15). The area under the first moment of the concentration-time curve from zero to infinity was estimated by the method of Smith and Schentag (31), which provides a means for calculating this parameter from steady-state data. Ceftazidime clearance was calculated by dividing the dose by the AUC. Tobramycin clearance was determined by multiplying the elimination rate constant by the volume of distribution (34).

Statistical analysis. Values are reported as means ± 1 standard deviation (SD). Pharmacokinetic and pharmacodynamic parameters were compared by using the two-tailed Student *t* test. Correlation of ceftazidime clearance with creatinine and tobramycin clearance was determined by using the Spearman correlation statistic. Significance was defined as a P of ≤ 0.05.

RESULTS

Susceptibility testing. The MICs of ceftazidime and tobramycin for the clinical *P. aeruginosa* isolate were 4 and 1 μg/ml, respectively. The MBCs were 4 and 4 μg/ml, respectively.

Patient demographics. A total of 14 patients were enrolled in the study. None of the patients received ceftazidime prior to enrollment in the study. One patient developed septic shock with renal compromise and was withdrawn 12 h after enrollment. Another patient had ceftazidime-resistant *Acinetobacter baumanii* isolated from a sputum culture and was withdrawn on the second day of the study. The demographics of the 12 evaluable patients (means ± SD) were as follows: age, 57 ± 12 years; sex, nine males and three females; APACHE II score, 15 ± 3; diagnosis, 9 of 12 patients with pneumonia. Isolates were recovered from six of the patients, consisting of *Escherichia coli* ($n = 1$), *Haemophilus influenzae* ($n = 1$), and *P. aeruginosa* ($n = 4$). The sources of these isolates were a urine specimen, a wound, and sputum specimens, respectively. Estimated creatinine clearance determined from serum creatinine did not significantly change in any patient between days 2 and 4 of the study (92 ± 29 versus 91 ± 33 ml/min). There was also no change in clearance of creatinine from the 24-h urine specimens during the study period (93 ± 53 versus 93 ± 59 ml/min).

Pharmacokinetic parameters. The pharmacokinetic parameters for ceftazidime continuous and intermittent infusions are listed in Table 1. The only parameter to show statistically significant differences between the two dosage regimens was the AUC, with intermittent administration achieving a larger value than continuous infusion ($P = 0.003$). During continuous infusion, 7 of the 12 patients maintained ceftazidime concentrations within the targeted range of 20 ± 5 μg/ml. Of the five patients who did not achieve the target concentration, two had ceftazidime steady-state concentrations between 10 and 14

TABLE 1. Pharmacokinetic and pharmacodynamic parameters

Parameter (unit)[a]	Value (mean ± SD)	
	Intermittent bolus	Continuous infusion
k_{el} (h^{-1})	0.268 ± 0.205	ND[b]
$t_{1/2}$ (h)	3.48 ± 1.61	ND
V (liters)	18.9 ± 9.0	ND
C_{max} (μg/ml)	124.4 ± 52.6	ND
C_{min} (μg/ml)	25.0 ± 17.5	ND
C_{ss} (μg/ml)	ND	29.7 ± 17.4
AUC (μg · h/ml)[c]	331 ± 165	112 ± 56
SBT at 24 h	1:4	1:4
T>MIC (%)	92	100
AUBC		
With tobramycin[c]	288 ± 151	115 ± 56
Without tobramycin	116 ± 85	104 ± 66

[a] k_{el}, elimination rate constant; $t_{1/2}$, half-life; V, volume of distribution; C_{max}, maximum concentration of drug in serum; C_{min}, minimum concentration of drug in serum; C_{ss}, steady-state concentration in serum.
[b] ND, not determined.
[c] $P = \leq 0.05$.

μg/ml and three had serum ceftazidime concentrations between 45 and 55 μg/ml. The patient with the ceftazidime half-life of <1 h had a range of steady-state concentrations of 5.5 to 13.6 μg/ml with an SD of 2.6 μg/ml. The other patient with the lower steady-state concentrations had a volume of distribution of 42 liters, and the range of concentrations was 9.7 to 12.0 μg/ml. The mean ceftazidime concentration-time profiles for each of the regimens are displayed in Fig. 1. The overall variability in concentrations in serum with continuous infusion was 17 μg/ml. However, on a per-patient basis, the SD of serum concentrations over 24 h was as follows: for five patients the SD was <5 μg/ml, for five patients the SD was 5 to 10 μg/ml, and for two patients the SD was 10 to 13 μg/ml. The two patients with the higher SD also had mean concentrations in serum of 34 to 36 μg/ml. The correlation coefficient (r) for ceftazidime clearance versus creatinine clearance from serum, 24-h urine collection, and tobramycin clearance were 0.42, 0.38, and 0.90, respectively. Tobramycin peak concentrations ranged from 7 to 20 μg/ml and were appropriate for each patient's infection, while all trough concentrations were <1.0 μg/ml.

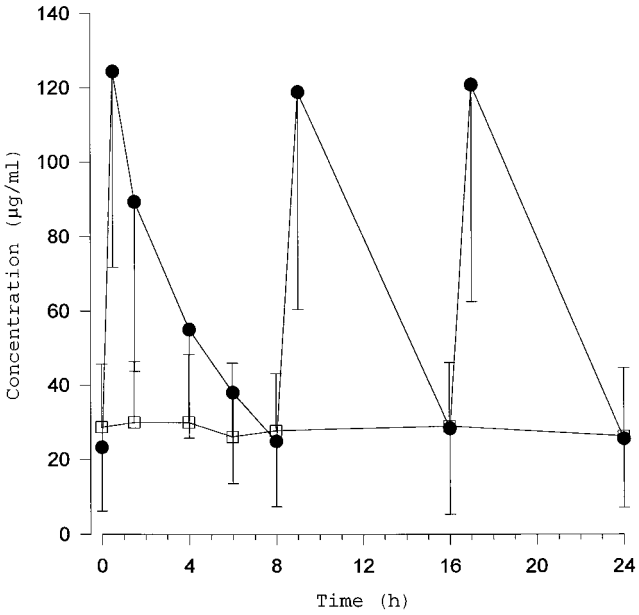

FIG. 1. Mean serum ceftazidime concentrations with SD (bars). ●, intermittent-bolus administration (2 g q8h); □, continuous-infusion administration (3 g over 24 h).

Pharmacodynamic parameters. The pharmacodynamic parameters for ceftazidime are summarized in Table 1. The 24-h SBTs were equal for the two regimens (1:4). The T>MIC was 100% for continuous infusion and 92% for intermittent bolus ceftazidime. With combination therapy, the AUBC was greater for patients receiving bolus administration than for the continuous-infusion groups ($P = 0.001$). However, after the tobramycin was eliminated from the serum samples, the AUBC was recalculated and no significant differences between the groups were found. One patient was excluded from both AUBC determinations because of an error in the infusion rate in which the patient received the 3-g dose of ceftazidime over 20 min during the continuous-infusion arm of the study. Tobramycin concentrations were undetectable (< 0.2 μg/ml) by TDx assay after the addition of the cellulose phosphate-binding resin.

Safety and tolerance of study drug. No adverse effects related to the drug or route of administration were observed in any patient during the study period.

DISCUSSION

A greater understanding of the pharmacodynamic properties of β-lactam antibiotics in the last decade has led investigators to reexamine the administration of these antimicrobial agents. With continuous-infusion therapy, one can maintain antibiotic concentrations at four or five times the MIC for the organism, at which maximal bactericidal activity occurs with the β-lactams. In contrast, with intermittent-bolus therapy, very high peak concentrations which do not add to the bactericidal activity of the drug are obtained. During the dosing interval, concentrations may often fall below the MIC for the pathogen(s) involved, and regrowth may occur. The efficacy of continuous infusion has been demonstrated in several in vitro models (6, 10, 23), animal studies (1, 19, 21, 29, 30, 32), and in humans (3, 12, 13, 17, 18).

Because β-lactams demonstrate concentration-independent killing, the ceftazidime T>MIC is crucial. In this study, the ceftazidime trough concentrations were greater than the MIC for 11 of 12 patients (92%) throughout the dosing period for the 2-g q8h regimen. In one patient, the ceftazidime concentration was below the limit of detection of the assay at 6 h after the first 2-g dose and at all subsequent trough time points. This was the only patient with a ceftazidime half-life of <1 h. In contrast, T>MIC was 100% for all patients receiving continuous infusions throughout the dosing period. Nicolau and colleagues (27) demonstrated similar results for 12 healthy volunteers receiving ceftazidime by 2- or 3-g continuous infusion over 24 h and intermittent injections, 1 g q8h or q12h, against clinical isolates of *P. aeruginosa* and *E. coli*. For all four regimens, the T>MIC was 100% against *E. coli*. Against the *P. aeruginosa* isolates (MIC, 4 μg/ml), the 1-g q8h and q12h regimens provided T>MICs of 82 and 52%, respectively, while the continuous-infusion regimens maintained a T>MIC of 100%.

Obtaining an appropriate drug concentration in relationship to the MIC for the infecting organism is a universally accepted concept as a goal of therapy. However, the parameter which best combines these concepts and predicts a successful outcome is subject to debate. Clinicians often compare single

antibiotic concentrations with the MIC in order to evaluate the efficacy of the treatment regimen. Researchers are debating whether the peak/MIC ratio, trough/MIC ratio, AUC/MIC ratio, and/or T>MIC is the parameter(s) with which to predict efficacy of treatment. The AUBC is a concept that utilizes the pharmacokinetics of the antibiotic over the desired dosing period along with the immune system components of the patients via their serum for SBT determination to calculate the killing activity (2).

Although our objective was to compare the bactericidal activities of the methods of administration for ceftazidime alone, it is standard practice in our institution to treat patients with suspected nosocomial gram-negative infections with combination therapy, often consisting of a β-lactam plus an aminoglycoside. We reported the SBT at 24 h for each regimen because at this time the tobramycin concentrations were <1.0 μg/ml (below the MIC) in all patients, which best represents ceftazidime monotherapy. In our study, the 24-h SBTs were equivalent for the two regimens at 1:4 with and without tobramycin. Unexpectedly, we found a significant difference between the AUBCs of intermittent administration and continuous infusion. We hypothesized that the tobramycin may have been significantly impacting upon our results. Although we attempted to maintain equivalent tobramycin concentrations during each arm of the study, there was variability within patients which may have affected our AUBC result. For this reason, we decided to eliminate the tobramycin by adding a binding resin to the patient's serum. After determining the SBTs in the absence of tobramycin, we recalculated the AUBC for each regimen and found no difference in AUBCs for the two methods of administration. These results are consistent with those of Nicolau and associates (27), who found no difference in the AUBCs between intermittent-bolus and continuous-infusion ceftazidime regimens for equal doses in healthy volunteers. They also demonstrated SBTs of ≥1:2 against *E. coli* and *P. aeruginosa* isolates throughout the dosing period. Our SBTs, however, were 1:4 on average at 1.5 and 24 h for both intermittent-bolus and continuous-infusion administration, consistently higher than those reported by Nicolau and colleagues.

The pharmacokinetic data of our study and others also support the use of continuous infusion. We maintained ceftazidime concentrations above the MIC in all 12 patients. Our steady-state concentration data are consistent with the results of a pharmacokinetic study by Castela et al. (8). Continuous-infusion ceftazidime was administered to critically ill patients at doses of 85 and 60 mg/kg/day. The observed mean steady-state concentrations (±SD) were 40 ± 18 and 25 ± 18 μg/ml, respectively. Mouton and colleagues (24) compared ceftazidime concentrations in blister fluid, using intermittent and continuous administrations. They found higher concentrations in blister fluid over time with continuous infusion than with intermittent-bolus administration. We observed greater variability between patients with regard to ceftazidime peak concentrations with intermittent administration than we did for continuous-infusion steady-state concentrations. These variations may be dependent on changes in fluid status and differences in volume of distribution among the patients. The range of volume of distribution for our patients was quite large (8 to 42 liters). The majority of our patients had a volume of distribution of approximately 18 liters; however, one patient previously had bilateral above-the-knee amputation, and the other was obese (132% above ideal body weight), which accounts for the extreme values.

We conclude that continuous infusion of ceftazidime consistently results in concentrations in serum above MICs of 4 μg/ml and may produce a more reliable serum drug concentration in critically ill patients with suspected gram-negative infections than intermittent administration. With continuous-infusion ceftazidime, we demonstrated an efficacy in pharmacodynamic parameters equal to that of intermittent administration while utilizing one-half the total daily dose. However, we did not evaluate the clinical efficacies of these different dosage regimens, and extrapolation of the results from this study should be cautioned.

ACKNOWLEDGMENT

We thank David Edwards at Wayne State University for assistance with the HPLC assay for ceftazidime concentrations.

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