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Once-Daily versus Twice-Daily Administration of Ceftazidime in the Preterm Infant

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Ceftazidime pharmacokinetics in 28 preterm infants (gestational ages, 25.6 to 31.9 weeks) were studied on day 3 of life. Patients with suspected septicemia were randomized on day 1 of life in two groups. One group ($n = 13$) was administered 25 mg of ceftazidime per kg of body weight once daily, and the other ($n = 15$) was given 25 mg of ceftazidime per kg twice daily. Both groups also received 25 mg of amoxicillin per kg twice daily. Blood samples were collected on day 3 of life with an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 h after an intravenous bolus injection. An additional blood sample was taken at 24 h from the group dosed once a day. High-performance liquid chromatography was used to determine serum ceftazidime concentrations. The pharmacokinetics of ceftazidime were best described by using a one-compartment model. The half-life for the elimination of the drug from serum, apparent volume of distribution, total body clearance of ceftazidime, and inulin clearance were not significantly different for both groups. The ceftazidime/inulin clearance ratio was 0.72 for both groups. However, trough concentrations in serum for the twice-daily group were significantly ($P < 0.001$) higher (42.0 ± 13.4 mg/liter) than those for the once-daily group (13.1 ± 4.7 mg/liter). The latter concentrations were all still substantially higher than the MIC of ceftazidime for major neonatal pathogens. We conclude that the currently recommended dosage of 25 mg of ceftazidime per kg twice daily for preterm infants with gestational ages below 32 weeks may be adjusted during the first days of life to one daily dose at 25 mg/kg, provided that for the empirical treatment of septicemia, amoxicillin at 25 mg/kg is also given twice daily.

Ceftazidime, an expanded-spectrum cephalosporin, is commonly used in the treatment of bacterial infections in the newborn (5). The currently recommended dosage regimen of ceftazidime for preterm infants less than 4 weeks old and whose birth weights are below 1,200 g is 25 to 100 mg/kg of body weight given intravenously twice daily (18). However, these dosage recommendations are based upon few pharmacokinetic data. Previous studies also did not stratify preterm infants according to gestational age (GA) or postnatal age, which has resulted in a substantial variability in pharmacokinetic parameters (3, 11–13, 17). We have previously demonstrated that the pharmacokinetic behavior of ceftazidime in preterm infants is strongly dependent on GA and postnatal age. At a dosage of 25 mg of ceftazidime per kg given intravenously twice daily, high trough levels were observed, especially in infants with GAs below 32 weeks (21). High concentrations of beta-lactam antibiotics in serum and tissues do not result in a more rapid killing of bacteria (4), but they may lead to neutropenia and the impairment of cellular and humoral immune responses (14). We therefore designed a prospective randomized study to evaluate the pharmacokinetic effects of reducing the dosage of ceftazidime from 25 mg/kg twice daily to 25 mg/kg once daily for preterm infants with GAs below 32 weeks.

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MATERIALS AND METHODS

Patients. Preterm infants ($n = 28$) admitted to the neonatal intensive care unit of the Sophia Children's Hospital between October 1991 and January 1992 with suspected or documented septicemia were enrolled in this study. The inclusion criteria were stability of hemodynamic function (a diuresis rate of >1 ml/kg/h and systolic and diastolic blood pressure above the third percentile [adjusted for GA]) and normal liver function. Infants receiving nephrotoxic or inotropic drugs were excluded. All infants had an indwelling arterial catheter. The GAs of the newborns were determined on the basis of the mother's menstrual history and were confirmed by early ultrasound examinations and by physical examination based on the criteria of Dubowitz et al. (7). The study protocol was approved by the Medical Ethical Committee of the University Hospital Rotterdam. Patients were enrolled only after informed consent was obtained from the parents. Eligible neonates were randomized at day 1 of life for 25 mg of ceftazidime per kg given intravenously once or twice daily in combination with 25 mg of amoxicillin per kg given intravenously twice daily. Patients with sterile cultures and without a focus of infection received a total of 72 h of antibiotic therapy. Patients with documented septicemia received at least 10 days of antibacterial treatment.

Pharmacokinetic study. The pharmacokinetics of ceftazidime were studied on day 3 after birth. Blood samples were taken from the indwelling arterial lines before the administration of an intravenous bolus injection of ceftazidime (time zero) and at 0.5, 1, 2, 4, 8, and 12 h afterwards. An additional blood sample was taken at 24 h for the once-daily group. Serum samples obtained after centrifugation (Merck type Eppendorf 5414; 3,000 × *g* for 1 min) were stored at −70°C.

Measurement of glomerular filtration rate. The glomerular filtration rate was measured on day 3 after birth by means of the continuous inulin infusion technique (22, 23).

Ceftazidime assay. Analysis of serum ceftazidime concentrations was performed by a modification of the high-performance liquid chromatography assay described by Ayrton (1). Concentrations of ceftazidime in serum were calculated from peak areas by comparison with those of standards in water containing 200, 100, 20, and 10 μg of ceftazidime per ml. Calibration curves were found to be linear over the range of 10 to 200 μg of ceftazidime per ml. The lower limit of detection of ceftazidime in serum was 0.5 mg/liter. The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of the ceftazidime, which had been incubated for 24 h at room temperature, was established.

TABLE 1. Demographic and clinical parameters for the infants in the once- and twice-daily treatment groups

Group (no.)	GA (wk)[a]	Birth wt (g)[a]	No. AGA/no. SGA[b]	Artificial ventilation (no. with/no. without)
Treated once daily (13)	29⅐ ± 2.0	1,168 ± 309	12/1	7/6
Treated twice daily (15)	29⅐ ± 2 1/7	1,141 ± 400	12/3	8/7

[a] Values are means ± standard deviations.
[b] AGA, appropriate size for GA; SGA, small for GA.

Pharmacokinetic analysis. Kinetic studies were performed on the third day of life. Visual inspection of individual model fits gave no indication that a more complex (e.g., two-compartment) pharmacokinetic model was required. Pharmacokinetic parameters were calculated with the multiple-dose equation described by Rowland and Tozer (19). The basic formula used was $C_t = \text{dose}/V \times (1 - r^N)/(1 - r) \times e^{-k\tau}$. In this formula, C_t is the concentration of ceftazidime in plasma at a given time t, V is the apparent volume of distribution, N is the dose number, and r is $e^{-k\tau}$, in which k is the elimination rate constant and τ is the dosing interval. For the twice-daily group, the ceftazidime concentration-versus-time curve was assumed to be attributable to the seventh dose (and the trough level at time zero was assumed to be attributable to the sixth dose). For the once-daily group, the ceftazidime concentration-versus-time curve was assumed to be attributable to the third dose (and the trough level at time zero was assumed to be attributable to the second dose). The data were weighted by calculating $1/(\text{predicted value})^2$. All calculations were carried out with the nonlinear regression module of SPSS/PC + V 4.0.1 (SPSS, Inc., Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

Statistical analysis. Data given are means ± standard deviations, unless indicated otherwise. The comparison of mean values was done by the unpaired Student t test. P values of ≤0.05 (two tailed) were considered significant.

RESULTS

Preterm infants ($n = 28$) were enrolled in this study. After randomization, 13 infants received 25 mg of ceftazidime per kg once daily and 15 were treated with 25 mg of ceftazidime per kg twice daily. All infants were also treated with 25 mg of amoxicillin per kg twice daily. Both groups appeared to be well matched on the basis of the demographic and clinical parameters of the patients (Table 1). All infants survived without any short- or long-term sequelae. Data for the pharmacokinetic parameters of ceftazidime and inulin clearance are given in Table 2. No significant differences between the predose blood sample and the poststudy dose trough concentration were found for the once-daily ($P = 0.92$) and twice-daily ($P = 0.89$) groups. Therefore, steady-state conditions were achieved. The ceftazidime/inulin clearance ratio was 0.72 for both groups. Glomerular filtration rates, as measured by inulin clearances, were similar in both groups and were all within the same range reported by us previously (21). Values for total body clearance, apparent volume of distribution, serum elimination half-life, and inulin clearance were not significantly different for both groups. Serum trough levels for the twice-daily group (42.0 ± 13.4 mg/liter) were significantly ($P < 0.001$) higher than those for the once-daily group (13.1 ± 4.7 mg/liter). The serum ceftazidime concentrations over time for both groups are depicted in Fig. 1.

DISCUSSION

The clearance rates for many compounds, including antibiotics, are much lower for preterm infants than for term infants. This can be attributed to the immaturity of renal function or the hepatic drug metabolism (9, 16). Pharmacokinetic studies are therefore necessary to optimize dosing regimens. We have previously demonstrated that the use of the lowest recommended dose for preterm infants, i.e., 25 mg of ceftazidime per kg given intravenously twice daily, resulted in high concentrations of ceftazidime in serum throughout the entire dosing interval (21). However, serious side effects were not seen. Nevertheless, high concentrations of ceftazidime may result in the inhibition of cell proliferation in cultured human myeloid precursor and lymphoid cells (14). This might lead to neutropenia and the impairment of cellular and humoral immune responses. In addition, a dose-dependent suppressive effect of beta-lactam antibiotics on the differentiation and proliferation of oligodendrocytes has been demonstrated in the rat model (20). We questioned the validity of the current dosage recommendations, and in a prospective, randomized way, we studied the pharmacokinetic effects of a dosage reduction from 25 mg of ceftazidime per kg twice daily to 25 mg/kg once daily for preterm infants with GAs below 32 weeks.

The data presented in this paper indicate that twice-daily dosing with ceftazidime leads to high serum trough concentrations (42.0 ± 13.4 mg/liter). Dosage reduction from twice daily to once daily results in a significant ($P < 0.001$) reduction in mean serum trough concentrations. However, the individual values (8.1 to 25.6 mg/liter) are still well above the MIC of ceftazidime for such major neonatal pathogens as *Streptococcus agalactiae* and *Escherichia coli* (8, 15). The therapeutic efficacy in animal models and for immunocompromised patients may be improved by the presence of concentrations of beta-lactam antibiotics in serum which continuously exceed the MIC (6, 25). This effect is achieved in adults by the continuous infusion of ceftazidime or by intermittent administration of high doses of ceftazidime two or three times daily. We show here that ceftazidime has such a prolonged half-life in preterm infants that once-daily administration of a low dose results in concentrations (8.1 to 25.6 mg/liter) that are above the MICs for major neonatal pathogens during the complete 24-h dosing interval.

Our data also indicate that the mean ceftazidime/inulin clearance ratios for both groups are similar (0.72). This is in agreement with the results of previous studies showing ratios of between 0.65 and 0.97 (2). The combination of a ceftazidime/inulin clearance ratio of 0.72 and the previously reported low (17%) protein binding suggests that renal elimination of ceftazidime is almost completely mediated by glomerular filtration (10). A recent study with adults indicated that in addi-

TABLE 2. Pharmacokinetic parameters of ceftazidime and inulin clearances of the infants in the once- and twice-daily treatment groups[a]

Group (no.)	CL (ml/h)	CL (ml/h/kg)	V (ml)	V (ml/kg)	$t_{1/2}$ (h)	CL_{in} (ml/h)	CL_{in} (ml/h/kg)
Treated once daily (13)	32.4 ± 10.9	27.8 ± 5.8	376 ± 120	323 ± 62	8.15 ± 1.18	45.0 ± 7.2	38.6 ± 3.8
Treated twice daily (15)	35.7 ± 16.8	30.8 ± 7.5	350 ± 138	305 ± 57	7.09 ± 1.66	49.8 ± 16.2	43.0 ± 7.2

[a] CL, clearance; V, apparent volume of distribution; $t_{1/2}$, elimination half-life; CL_{in}, inulin clearance. Values are means ± standard deviations.

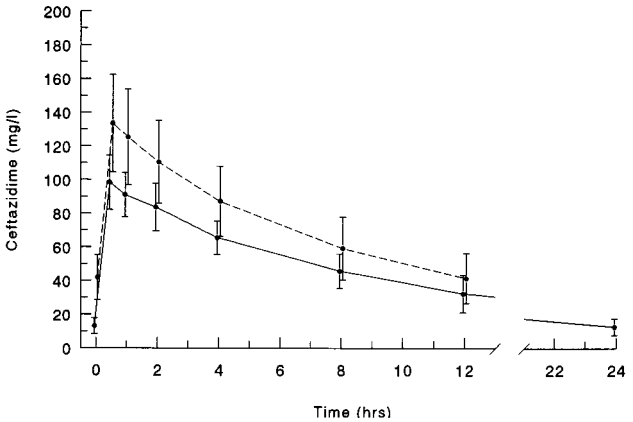

FIG. 1. Serum ceftazidime concentrations (means ± standard deviations) over time for once-daily (solid line) and twice-daily (dotted line) treatment groups.

tion to glomerular filtration, some tubular excretion of ceftazidime, which is probably triggered by passive reabsorption, occurs (24). At this moment, data on tubular excretion of ceftazidime in the preterm infant are not available. In our study, the coadministration of amoxicillin might have led to the inhibition of tubular transport of ceftazidime by competition.

We conclude that the recommended twice-daily administration of ceftazidime in preterm infants with GAs below 32 weeks may be adjusted to once-daily dosing in the first days of life. Alternatively, twice-daily dosing with doses lower than 25 mg/kg might even lead to an increased therapeutic effect compared with that of once-daily dosing at 25 mg/kg (4, 14). However, for the empirical treatment of neonatal septicemia, amoxicillin (at 25 mg/kg twice daily) should be added to the antibiotic treatment protocol. These dosage recommendations cannot yet be applied to infants with suspected or documented meningitis, since data on the penetration of cerebrospinal fluid in infants with once-daily dosing are missing.

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