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

JOHN N. VAN DEN ANKER,1* RIK C. SCHOEMAKER,2 BERT J. VAN DER HEIJDEN,3 HENRIETTE M. BROERSE,1 HERMAN J. NEIJENS,1 AND RONALD DE GROOT1

Department of Pediatrics, Erasmus University and University Hospital Rotterdam/Sophia Children’s Hospital, Rotterdam,1 Centre for Human Drug Research, Leiden,2 and Department of Pediatrics, Juliana Children’s Hospital, The Hague,3 The Netherlands

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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 per day 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.

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 isotropic 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

<table>
<thead>
<tr>
<th>Group (no.)</th>
<th>GA (wk)*</th>
<th>Birth wt (g)*</th>
<th>No. AGA/no. SGA*</th>
<th>Artificial ventilation (no. with/no. without)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated once daily (13)</td>
<td>29.5 ± 2.0</td>
<td>1,168 ± 309</td>
<td>12/1</td>
<td>7/6</td>
</tr>
<tr>
<td>Treated twice daily (15)</td>
<td>29.5 ± 2.5</td>
<td>1,141 ± 400</td>
<td>12/3</td>
<td>8/7</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations.

Table 2. Pharmacokinetic parameters of ceftazidime and inulin clearances of the infants in the once- and twice-daily treatment groups

<table>
<thead>
<tr>
<th>Group (no.)</th>
<th>CL (ml/h)</th>
<th>CL (ml/h/kg)</th>
<th>V (ml)</th>
<th>V (ml/kg)</th>
<th>t(1/2) (h)</th>
<th>CLum (ml/h)</th>
<th>CLum (ml/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated once daily (13)</td>
<td>32.4 ± 10.9</td>
<td>27.8 ± 5.8</td>
<td>376 ± 120</td>
<td>323 ± 62</td>
<td>8.15 ± 1.18</td>
<td>45.0 ± 7.2</td>
<td>38.6 ± 3.8</td>
</tr>
<tr>
<td>Treated twice daily (15)</td>
<td>35.7 ± 16.8</td>
<td>30.8 ± 7.5</td>
<td>350 ± 138</td>
<td>305 ± 57</td>
<td>7.09 ± 1.66</td>
<td>49.8 ± 16.2</td>
<td>43.0 ± 7.2</td>
</tr>
</tbody>
</table>

* CL, clearance; V, apparent volume of distribution; t(1/2), elimination half-life; CLum, inulin clearance. Values are means ± standard deviations.
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 an 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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REFERENCES


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