Pharmacokinetics of Ceftizoxime

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Summary. The kinetics of ceftizoxime, a newly developed cephalosporin, were evaluated in 6 healthy subjects, with respect to its excretory pathways especially by the biliary route. Total, renal and biliary clearance were determined at two different steady states. Steady state was achieved by constant intravenous infusion (604.1 mg/h) over 6 h after an initial loading dose (750 mg); 1.5 h after discontinuation of that infusion, a further infusion was commenced at a lower rate (284 mg/h) over 3 h, the second steady state being reached 0.5 to 1.0 h later.

The drug was mainly excreted by the kidneys (56.7 to 92.9% of the dose). Biliary excretion, measured by the duodenal perfusion and marker dilution technique, was low (0.2 to 7.8% of the dose). Urinary and biliary excretion as well as total clearance were not dose-dependent. However, there was pronounced interindividual variation in total (35.2 to 236 ml/min) and renal clearance (10.6 to 208 ml/min), which could both be explained by varying interindividual urinary flow rates (mean flow rate: 0.99 ml/min to 3.14 ml/min).

Intraindividual variation in renal clearance was less pronounced, but in the same subject changes in renal clearance were correlated with changes in urinary flow rate. From the varying renal clearance, which exceeded the glomerular filtration rate at high urinary flow rates and was below it at low urinary flow rates, it can be concluded that, in addition to glomerular filtration, tubular secretion and tubular reabsorption are involved in the renal excretion of ceftizoxime.

The half-life calculated from two point estimates after discontinuation of the infusion at the higher rate tended to be longer in subjects with high total clearance (e. g. 1.4 h, clearance 223 ml/min) and shorter in subjects with low total clearance (e. g. 0.85 h, clearance 35.2 ml/min). From this it is concluded that the true half-life was not observed after discontinuation of the infusion.

Key words: ceftizoxime, cephalosporins; renal excretion, tubular reabsorption, tubular secretion, healthy volunteers, biliary excretion, clearance studies

Ceftizoxime is a newly developed antimicrobial substance of the cephalosporin group now being used in therapy. Its chemical structure is related to cefotaxime, differing by lack of the acetomethyl-group at C-3 (Fig. 1).

In previous reports on the kinetics of ceftizoxime, the half-life was stated to range between 1.3 and 1.4 h, and renal excretion accounted for approximately 90% of the total clearance (Dubb et al. 1982; Nakashima et al. 1981; Onkawa et al. 1982; Peterson et al. 1982). Levels of the drug were measured in bile from surgical patients (Helm et al. 1982) and it was concluded that the remainder of the drug was excreted by the biliary route. Quantification of biliary excretion was not possible with the method used in the study by Helm et al. (1982).

The aim of the present study was to reevaluate the kinetics of ceftizoxime with respect to its biliary excretion. The kinetics during two different steady-state concentrations were investigated.

Fig. 1. Structure of ceftizoxime
Table 1. Details of the subjects characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Mean urinary flow rate (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>69</td>
<td>192</td>
<td>112.0</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>75</td>
<td>175</td>
<td>103.2</td>
<td>1.94</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>72</td>
<td>177</td>
<td>130.0</td>
<td>1.02</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>60</td>
<td>176</td>
<td>88.0</td>
<td>1.26</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>69</td>
<td>184</td>
<td>91.8</td>
<td>2.28</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>75</td>
<td>178</td>
<td>98.7</td>
<td>3.14</td>
</tr>
</tbody>
</table>

a calculated by the method of Cockcroft and Gault (1976);

b mean 0–10.5 h

Materials and Methods

Subjects

Six healthy male subjects volunteered for the study and gave written consent after being informed of its aims and risks. Approval for fluoroscopy was given by the Innenministerium, Baden-Württemberg, FRG. Before entering the study the subjects underwent clinical examination, including ECG and laboratory tests (liver enzymes, creatinine, urea, electrolytes, whole blood count, urine analysis), which all were within the normal range. Details of age, height, weight and creatinine clearance of the subjects are given in Table 1.

Procedure

Ceftizoxime was supplied by Boehringer, Mannheim FRG. Solutions for the intravenous injection and infusion were prepared by dissolving the substance in sterile saline. In order to obtain an immediate steady state plasma concentration, ceftizoxime was given by intravenous bolus injection (750 mg) followed by an intravenous infusion (mean dose of Subjects 2–6) 604 mg/h) over 6 h. The infusion was then stopped for 1.5 h. Then a further infusion was given at the rate of 284 mg/h (mean dose in Subjects 2–6) for a further 3 h. The infusion was administered through an indwelling venous catheter by a calibrated pump (Perfusor, Braun Melsungen, FRG). In Subject 1 the infusion rates were 319 mg/h over 6 h and 192 mg/h over 3 h, separated by a 1.5 h interval without drug. Saline was infused over the period of 10.5 h at a constant rate (0.4 l/h), to supply fluid.

Specimen Sampling

Blood (10 ml samples) was withdrawn from a contralateral antecubital arm vein before and 4.5, 5, 5.5, 6, 7.5, 8, 8.5, 9, 9.5, 10 and 10.5 h after bolus injection of the loading dose. Serum was separated by centrifugation and was stored at −20°C until analysis.

Urine fractions were collected up to 24 h, the volume and pH were recorded for each sample and an aliquot was stored at −20°C until analysis.

Biliary excretion of the drug was measured using the duodenal perfusion and marker dilution technique (Gundert-Remy et al. 1982). Samples of duodenal aspirate were collected hourly for the first 3 h and thereafter every 0.5 h. According to previous investigations (Gundert-Remy et al. 1982) steady-state biliary excretion was not expected to occur until 4.5 h after commencement of the study, so blood samples were not taken before that time.

Determination of Ceftizoxime

The concentration of ceftizoxime in serum, urine and infusion solution was measured by HPLC. To 200 µl of serum a mixture of perchloric acid and methanol (2/1, V/V) was added. After mixing (Vortex, 30 s) and centrifugation at 4°C, 20 µl of the clear supernatant was injected into the HPLC (Biotronic, Duesseldorf, FRG). The separation column (stainless steel, 12.5 cm × 0.25 cm, 4.9 mm inner diameter) was filled with Spherisorb 5 ODS and was held at 10°C. The sample was eluted with tetraethylammonium hydrochloride (pH 2.8)/acetonitrile (90/10) at the rate of 2 ml/min. Detection of the substance was done by UV-spectrometry at 260 nm. Retention time was 2.8 min for the unchanged substance. Because of the sharpness of the peak, peak height was chosen for quantification.

Duodenal samples were treated in the same manner as serum samples.

Urine samples and infusion solutions were analysed after appropriate dilution with distilled water. To 500 µl of diluted urine 500 µl of a mixture of perchloric acid and methanol (see above) was added and mixed.

After centrifugation, 20 µl of the supernatant was injected into the HPLC apparatus.

Calibration curves were constructed by adding ceftizoxime to the biological fluids so that concentrations up to 150 mg/l (serum, duodenal aspirate) and 3.0 g/l (urine, solutions for infusion) were produced. The lower limit of detection was 0.05 mg/l. The recovery was between 92.3% and 98.4%, depending on concentration and biological material. The precision was 96.1 ± 3.2% (5 determinations in parallel) and the reproducibility was 94.7 ± 4.2% (mean standard deviation over 5 days).

Calculations

Steady-state concentrations were calculated as the arithmetic mean of subsequent serum concentrations beginning with the concentration which did not dif-