The Intravitreal Penetration of Ceftriaxone in Man following Systemic Administration

Mordechai Sharir, † Giora Triesrer, † J. Kneer, ‡ and Ethan Rubinstein*

Seventeen patients who underwent vitreal surgery received ceftriaxone (Rocephin) 1–2 g intramuscularly at various time intervals before surgery. Specimens of serum and vitreous were assayed for ceftriaxone concentrations both by bioassay and high pressure liquid chromatography. All patients had detectable vitreous (and serum) ceftriaxone concentrations at all time periods. Vitreous ceftriaxone levels at the first 4.5 hr following the administration of the antibiotic ranged from 1.4–19.4 μg/ml and averaged 5.9 μg/ml. At 12–13 hr following ceftriaxone administration vitreous concentrations were 11.5 (± 9.0) μg/ml. Ceftriaxone in intramuscular administration could be used as prophylaxis against ceftriaxone-susceptible microorganisms in vitreal surgery. Ceftriaxone is the first antibiotic for which reliable penetration into the vitreous is demonstrable following intramuscular administration. Invest Ophthalmol Vis Sci 30:2179–2183, 1989

Ceftriaxone is a third-generation cephalosporin that possesses activity against a wide range of microorganisms. It inhibits most enterobacteria in concentrations of 1 μg/ml or less.1,2 The MIC90 against Staphylococcus aureus is around 6.0 μg/ml whereas most other gram-positive cocci (with the exclusion of Staphylococcus epidermidis and Streptococcus faecalis) are inhibited by less than 3.0 μg/ml.1,2 Its MIC90 against Pseudomonas aeruginosa, Acinetobacter sp., chlamydia and Bacteroides sp. is 32.0 μg/ml or higher.1

One of the more interesting features of ceftriaxone is its prolonged plasma levels—the mean plasma elimination half-life being 8 hr. Thus a single daily dose may lead to bactericidal levels at most sites of infections for a period of 24 hr.1,3

Recent reviews of bacterial endophthalmitis have stressed the increasing importance of gram-negative organisms as pathogens. In particular Proteus mirabilis, indole-positive Proteus sp., Pseudomonas aeruginosa, Haemophilus influenzae and Klebsiella sp. have been isolated frequently.4–6 Gram-positive organisms, and in particular Staphylococcus epidermis have been isolated frequently from cases of bacterial endophthalmitis associated with intraocular lenses.7,8

The following study of ceftriaxone concentrations in the human vitreous was undertaken in view of such aspects as the drug's very high serum levels compared to the MIC,1 the adequate penetration of ceftriaxone into several body fluids, including the cerebrospinal fluid, following systemic administration,9,10 the therapeutic concentrations obtained in the aqueous humor following 1–2 g intravenous single doses,11 the prolonged serum half-life3 and the favourable clinical experience in a variety of bacterial infections in man.1,12

Materials and Methods

Excluded from the study were patients with a history of allergy to cephalosporins; patients with renal insufficiency; patients who received any antibiotic in the preceding 2 weeks; and those with recent (4 weeks) ocular trauma. Twenty-three patients were included in the study. Their ages ranged from 11 to 80 years. All patients had serum creatinine levels below 2 mg/dl before entering the trial (one patient, No. 18, had chronic active hepatitis).

Indications for operations in the seventeen evaluable patients were as follows:

- Proliferative vitreous retinopathy (PVR) with retinal detachment—one patient with diabetes mellitus—all secondary operations—five cases.
- Total retinal detachment—three cases.
- Intraocular foreign body—two cases.
• Retinal detachment with high myopia—three cases.
• Preretinal membrane—two cases.
• Vitreal hemorrhage—two cases.

Five of these patients had diabetes mellitus, one case as the underlying disorder, and three patients had aphakia. Four patients were excluded from the final analysis because of the presence of hemorrhagic or heavily xanthochromic vitreal samples, leaving 17 patients for the final analysis.

After an informed consent had been obtained from the patients or their legal guardians, 15 patients received ceftriaxone 2 g intramuscularly, five to six doses every 12 hr in order to reach a steady state, the last dose being given 1.5 hr to 13 hr before the operation. This dosage is considered indicated for severe systemic infections. The dosage for moderate systemic infections being 2 g once daily administered i.m. or i.v. Due to the long half-life of the antibiotic, an attempt was made to enroll the patients into two groups, those that received the last dose 1.5-4.5 hr before operation and those that received the last administration 12-13 hr before surgery. Two young patients (11 and 15 years old) received 1 g intramuscularly (2 hr and 2.5 hr before surgery). All patients received prior to that five to six doses (2 g and 1 g) intramuscularly every 12 hr in order to reach a steady state.

All surgery was performed by one surgeon (GT). Surgery included the creation of a fornix-based conjunctival flap. A 1 mm sclerotomy was made 4 mm from the temporal limbus, through which an Ocutome probe was then inserted into the vitreal space. Vitreous humor samples, approximately 0.5 ml, were cut and sucked into special containers through the probe. There was no dilution of the obtained vitreous sample that was used for antibiotic concentration determination.

Samples were obtained 15 to 20 min after the beginning of the operation. At the time of vitreal sampling, a blood specimen was obtained from the antecubital vein. Vitreal samples that contained visible blood were discarded and only clear or slightly xanthochromic samples were analyzed.

Vitreal specimens were sonicated on ice for 30 sec. Vitreous specimens that did not completely liquify following the sonication were not included (two patients). Serum was immediately separated from whole blood by centrifugation and frozen at −20°C until assay. Ceftriaxone was assayed in the serum and in the vitreous humor by bioassay, which measured the entire antibacterial activity, and by high performance liquid chromatography (HPLC).

In the bioassay, which was performed in triplicate, the agar disc diffusion was used with *Escherichia coli* ATCC 11105 on Tryptic Soya Agar (Difco, USA) incubated for 12 hr at 37°C. The minimal level of ceftriaxone detection by bioassay was 0.8 µg/ml and the maximum 200 µg/ml in undiluted specimen; the sensitivity was 0.1 µg/ml for concentrations in the therapeutic range.

HPLC was performed according to the method of Trautmann et al., the column used was a Lichrosorb RP-18, 150 × 3.2 mm, and the mobile phase was acetonitrile 44% in tetraoctylammonium bromide. The minimal detection limit was 0.5 µg/ml and the coefficient of variation 0.7–13%.

<table>
<thead>
<tr>
<th>Table 1. Serum and vitreous ceftriaxone levels following intramuscular administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
</tr>
<tr>
<td>5.</td>
</tr>
<tr>
<td>6.</td>
</tr>
<tr>
<td>7.</td>
</tr>
<tr>
<td>8.</td>
</tr>
<tr>
<td>9.</td>
</tr>
</tbody>
</table>

* PVR: Proliferative vitreoretinopathy. † S/P: Status post.
Table 2. Serum and vitreous levels of ceftriaxone following intramuscular administration 1–4 hr before surgery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Bioassay</th>
<th>HPLC</th>
<th>Bioassay</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.4</td>
<td></td>
<td>≥200</td>
<td>170</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>19.4</td>
<td>≥200</td>
<td>135</td>
</tr>
<tr>
<td>3</td>
<td>5.3</td>
<td>10.4</td>
<td>≥200</td>
<td>176</td>
</tr>
<tr>
<td>4</td>
<td>2.8</td>
<td>6.3</td>
<td>≥200</td>
<td>135</td>
</tr>
<tr>
<td>5</td>
<td>11.6</td>
<td>10.4</td>
<td>≥200</td>
<td>140</td>
</tr>
<tr>
<td>6</td>
<td>1.4</td>
<td>1.4</td>
<td>≥200</td>
<td>122</td>
</tr>
<tr>
<td>7</td>
<td>1.7</td>
<td>1.7</td>
<td>≥200</td>
<td>114</td>
</tr>
<tr>
<td>8</td>
<td>4.1</td>
<td>4.1</td>
<td>≥200</td>
<td>140</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>15.3</td>
<td>5.9 (±5.5)</td>
<td>200</td>
<td>141.5 (±20.0)</td>
</tr>
</tbody>
</table>

To insure the reliability of our assay, vitreous from patients undergoing surgery but not receiving antibiotics was spiked with ceftriaxone in concentrations of 0.5–50 μg/ml.

The results of the HPLC and bioassay were in the range of ±15% for HPLC and ±12% for the bioassay for this range of concentrations. The standard error for the bioassay in vitreous was 2.9 and in serum 1.9; for the HPLC it was 1.2 in vitreous and 4.5 in serum.

Results

Seventeen patients received intramuscular ceftriaxone 1–2 g every 12 hr for 48 hr prior to planned surgery. This regimen was chosen in order to achieve a kinetic steady state. The last ceftriaxone dose was administered 90 min–13 hr prior to the planned surgery (Table 1).

All the patients had detectable ceftriaxone in their serum and vitreous humor measurable both by the bioassay and HPLC methods. The microbiological assay measures the entire amount of the drug and its metabolite capable of inhibiting bacterial growth while the HPLC method measures the actual concentration of the parent compound.

Mean serum ceftriaxone level in the first 4.5 hr following the antibiotic administration was ≥200 μg/ml when measured by bioassay and 14.5 μg/ml when measured by HPLC (Table 2). Simultaneous vitreous ceftriaxone levels ranged from 1.4–21 μg/ml and averaged 5.9 μg/ml measured by HPLC. At 12–13 hr following ceftriaxone administration mean serum levels were 46.1 (±20.4) μg/ml measured by bioassay while mean vitreous levels were 5.1 μg/ml as measured by HPLC and 11.5 (±9.0) μg/ml as measured by the bioassay method (Table 3).

Discussion

Our present data suggest that following intramuscular ceftriaxone administration, this antibiotic is detectable in therapeutic concentrations in the vitreous. This observation stands in sharp contrast to our experience with cefotaxime.14 In five patients in whom cefotaxime 1 g was administered intramuscularly, no cefotaxime or its major metabolite desacetyl cefotaxime could be detected in the vitreous 45–240 min following administration, while serum levels were in the therapeutic range (2.0–31.5 μg/ml).14 Similarly, gentamicin also reached subtherapeutic levels (<0.2 μg/ml) in the uninfected human vitreous following systemic administration.15 Limited information on other antibiotics such as beta-lactam and macrolide suggests, along the same line, unsatisfactory antibiotic penetration into the human vitreous following systemic administration.16 The situation may be somewhat different with the quinolones in a new class of broad spectrum oral antibiotics, as suggested by isolated reports.17 This situation with beta-lactam antibiotics (eg, cephalosporins, penicillins and carbapenem) in humans, which is further supported by similar data in experimental animals,18–20 has led to the recommendation of intravitreal administration of antibiotics as the therapy of choice in cases of bacterial endophthalmitis.21,22

Table 3. Serum and vitreous levels of ceftriaxone following intramuscular administration 12–13 hr before surgery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Bioassay</th>
<th>HPLC</th>
<th>Bioassay</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>11</td>
<td>5.4</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>28</td>
<td>3.7</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>6.1</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>7.6</td>
<td>22.0</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4.2</td>
<td>4.2</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3.5</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4.0</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>11.5 (±9.0)</td>
<td>5.1</td>
<td>46.1 (±20.4)</td>
<td>64</td>
</tr>
</tbody>
</table>
The concentrations obtained in the vitreous humor in our patients are expected to inhibit effectively \textit{Streptococcus pneumoniae} and \textit{Streptococcus pyogenes} but to be only marginally effective against \textit{Staphylococcus aureus} and \textit{Staphylococcus epidermis} (Table 4).\(^1\) Most gram-negative organisms except \textit{Pseudomonas aeruginosa}, \textit{Enterobacter sp.} and \textit{Acinetobacter sp.} should be effectively killed by the obtained intravitreal ceftriaxone concentrations (Table 4).\(^1\) The highest vitreal concentrations in our patients were obtained in an aphakic patient (No. 11) as well as in patients (not included) with hemorrhagic vitreous. All other patients had vitreal ceftriaxone levels ranging from 1.4–10.4 \(\mu\)g/ml (measured by HPLC). These levels represent 5–10% of mean corresponding serum levels and are similar to ceftriaxone levels observed in the cerebrospinal fluid following systemic administration.\(^{23,24}\) These levels in the vitreous are significantly higher than those observed in the aqueous humor and tears 1–4 hr following a single 1 g’ administration.\(^{1,11,22}\) This difference may be due to the larger dose employed by us and to the fact that our study was performed with the patients in a steady state and not following a single antibiotic administration.

Beta-lactam antibiotics have been reported to be eliminated in the primate and the rabbit vitreous by an active transport mechanism, located in the retina. This transport mechanism can be inhibited by probenecid and inflammation.\(^{16,20}\) This elimination process in our cases probably was affected adversely by the inflammatory conditions in the vitreous associated with the diseases that comprised the indications for surgery. This issue could not be addressed in the present study because of the single sampling of the vitreous. It is conceivable, however, that in cases of bacterial endophthalmitis in which the eliminating mechanism is more damaged than in the present cases even higher ceftriaxone concentrations can be expected in the vitreous.

Most of our cases had advanced disease, indicating the need for surgery, or had had previous vitreal procedures. In both conditions the blood–retinal barrier was altered and penetration of antibiotics into the vitreous might have been altered. Still, patients Nos. 5 and 12 in this series had a preretinal membrane, a condition that does not alter the blood–retinal barrier, and had had no previous surgery, but had vitreal levels in the range observed in the other patients (10.4 and 3.7 \(\mu\)g/ml), suggesting that ceftriaxone penetrates well into the vitreous humor in cases of intact blood–retinal barrier as well.

In conclusion, our results suggest that ceftriaxone by intramuscular administration is the first antibiotic that appears to penetrate into the vitreous in concentrations that therapeutic for many ocular pathogenic microorganisms. This conventional and easy-to-administer route of administration may theoretically spare the patient painful subconjunctival antibiotic injections or intravitreal therapy. Clinical trials are needed, however, in order to assess this issue.

\textbf{Key words:} vitreous, penetration, ceftriaxone, human, therapy

\textbf{References}


\begin{table}
\centering
\caption{In vitro activity of ceftriaxone against common ocular pathogens}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Species} & \textbf{No. Tested} & \textbf{MIC}_{50}\textsuperscript{*} (\(\mu\)g/ml) & \textbf{MIC}_{90}\textsuperscript{*} (\(\mu\)g/ml) \\
\hline
\textit{Streptococcus pyogenes} & 40 & 0.03 & 0.03 \\
\textit{Staphylococcus epidermidis (MS)}\textsuperscript{†} & 22 & 6.3 & 50 \\
\textit{Staphylococcus epidermidis (MR)}\textsuperscript{‡} & 30 & 64 & 64 \\
\textit{Staphylococcus aureus (MS)} & 10 & 3.5 & 9.7 \\
\textit{Staphylococcus aureus (MR)} & 189 & 64 & 128 \\
\textit{Haemophilus influenzae} & 242 & 0.005 & 0.008 \\
\textit{Klebsiella sp.} & 92 & 0.06 & 0.1 \\
\textit{Proteus mirabilis} & 184 & 0.005 & 0.01 \\
\textit{Proteus indole pos.} & 373 & 0.02 & 0.3 \\
\textit{Pseudomonas aeruginosa} & 4.7 & 12 & 38 \\
\hline
\end{tabular}
\textsuperscript{*} \textbf{MIC}_{50} \text{ and } \textbf{MIC}_{90} \text{ are the means of the lowest concentration inhibiting growth of 50\% \text{ and } 90\% \text{ of the organism tested}.}
\textsuperscript{†} \textbf{Methicillin-sensitive.}
\textsuperscript{‡} \textbf{Methicillin resistant.}
\end{table}


