Comparative Pharmacokinetics and Dosage Regimen of Cefepime in Buffalo Calves
(*Bubalus bubalis*) following Intravenous and Intramuscular Administration

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**Abstract**

The disposition kinetics and dosage regimen of cefepime were compared after its intravenous and intramuscular administration at 10 mg.kg⁻¹ in healthy buffalo calves. The drug concentration in plasma was estimated by microbiological assay. The peak plasma concentration of cefepime after intravenous injection was at 1 min (46.4 ± 0.40 µg.ml⁻¹) and after intramuscular administration it was at after 45 min (24.0 ± 0.30 µg.ml⁻¹). The elimination half-life following intravenous and intramuscular administration were 2.75 ± 0.06 h and 2.46 ± 0.004 h, respectively. To maintain a minimum therapeutic concentration of cefepime as 1.0 µg.ml⁻¹, a satisfactory dosage regimen of cefepime should be 11.0 mg.ml⁻¹ for intravenous and 14.8 mg.ml⁻¹ for intramuscular administration repeated at 12 h intervals.

**Keywords:** Pharmacokinetic, cefepime, intravenous, intramuscular.

Cefepime is a parenteral, fourth generation cephalosporin antibiotic with a broader spectrum of antimicrobial activity than other cephalosporins and non-traditional β-lactam antibiotics. It has potent bactericidal activity against a broad range of gram-negative and gram-positive organisms. It has the advantage over third generation cephalosporins of having activity against *Pseudomonas* species and excellent activity against the *Enterobacteriaceae* including many strains resistant to third generation cephalosporins and aminoglycosides (Fusch *et al.*, 1985). Like other cephalosporins and penicillins, cefepime inhibits third and final stages of bacterial cell wall synthesis by preferentially binding to specific penicillin binding proteins (PBPs) that are located inside the bacterial cell wall (Neu, 1985). In this study, a comparison of pharmacokinetic parameters and doses regimen of cefepime following intravenous and intramuscular administration in buffalo calves was done.

**Materials and Methods**

Four male buffalo calves of 6 to 12 months age were used for the experiment. The experimental protocol followed the ethical guidelines on the proper care and use of animals. Cefepime hydrochloride (Unichem Laboratories, Mumbai) was injected intravenously at the dose rate of 10 mg.kg⁻¹ body weight. Blood samples (5-6 ml each) were collected from jugular vein before administration and at 1, 2.5, 5, 7.5, 10, 15, 30, 45, 60 min and 2, 3, 4, 5, 6, 8, 10, 12, 24 and 36 h after administration of cefepime. Plasma from samples were separated and stored at −20°C till analysis. Same drug with the same dose was administered intramuscularly in the same group of animals after a 20 day washout period after experiment by intravenous route. Before repeating the drug in the same animals, the blood samples were collected to ensure that there were no traces of drug. The concentration of cefepime in plasma was estimated by using the microbiological assay technique (Arret *et al.*, 1971). The plasma concentration time data for each calf were determined according to the least squares regression technique. Pharmacokinetic parameters were calculated manually by the computed least-square linear regression technique (Gibaldi and Perrier, 1982). Based on kinetic data the dosage regimen of cefepime were determined.
Results and Discussion

Disposition of cefepime in plasma after i/v administration fitted a two-compartment open pharmacokinetic model and following i/m administration, it can be best fitted to one-compartment open model. The pharmacokinetic parameters obtained after i/v and i/m administration of cefepime in buffalo calves are compared in Table I.

There was no significant difference in the values of pharmacokinetic parameters, AUC, AUMC, Vd\textsubscript{area}, Cl\textsubscript{B} and MRT following i/v and i/m administration. Elimination of cefepime was slow with an elimination half-life ($t_{1/2}\beta$) 2.46 ± 0.004 h following i/v injection in buffalo calves (2.75 ± 0.06 h). The total body clearance (Cl\textsubscript{B}) of cefepime following i/v administration was 0.139 ± 0.002 L.kg\textsuperscript{-1}.h\textsuperscript{-1}. Similar value of total body clearance of 0.139 ± 0.001 L.kg\textsuperscript{-1}.h\textsuperscript{-1} was obtained when cefepime was given intramuscularly to the buffalo calves.

While comparing the dosage regimens of cefepime in calves by i/v and i/m route of administration, it was revealed that to maintain the minimum therapeutic plasma levels, a higher dosage is required after i/m injection (14.8 followed by 14.3 mg.kg\textsuperscript{-1} b.wt. at 12 h intervals) as compared to i/v injection (11.5 followed by 11 mg.kg\textsuperscript{-1} b.wt at 12 h intervals). Lack of any significant adverse effect, rapid absorption, high value of AUC, volume of distribution and bioavailability revealed that i/m. administration of cefepime is as good as i/v injection in the treatment of mild to moderate bacterial infections. However, in severe infections, where initially high diffusion gradient is desired, the importance of first injection by i/v route cannot be ruled out.

Summary

Following single i/m. administration of cefepime in buffalo calves, the drug was rapidly absorbed from i/m. injection site. The values of elimination half-life, total duration of pharmacological effect (td) and tissue/plasma ration (T/P) were significantly lower after i/m administration of cefepime as compared to its i/v administration. The mean value of AUC, AUMC, Vd\textsubscript{area}, Cl\textsubscript{B} and MRT were almost same after i/v and i/m injections of cefepime.

References


### Table I. Comparative pharmacokinetics of cefepime following its single intravenous and intramuscular administration at the dose of 10 mg.kg\textsuperscript{-1} body weight in healthy buffalo calves (n=4).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Intravenous</th>
<th>Intramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}\beta$</td>
<td>h</td>
<td>2.75±0.06</td>
<td>2.46±0.004*</td>
</tr>
<tr>
<td>AUC</td>
<td>μg.ml\textsuperscript{-1}.h</td>
<td>70.2±0.52</td>
<td>69.9±0.50</td>
</tr>
<tr>
<td>AUMC</td>
<td>μg.ml\textsuperscript{-1}.h\textsuperscript{2}</td>
<td>265.1±3.33</td>
<td>269.0±2.63</td>
</tr>
<tr>
<td>Vd\textsubscript{area}</td>
<td>L.kg\textsuperscript{-1}</td>
<td>0.57±0.01</td>
<td>0.51±0.003</td>
</tr>
<tr>
<td>Cl\textsubscript{B}</td>
<td>L.kg\textsuperscript{-1}.h\textsuperscript{-1}</td>
<td>0.139±0.002</td>
<td>0.139±0.001</td>
</tr>
<tr>
<td>MRT</td>
<td>h</td>
<td>3.77±0.06</td>
<td>3.84±0.01</td>
</tr>
<tr>
<td>td</td>
<td>h</td>
<td>9.16±0.19</td>
<td>8.19±0.07*</td>
</tr>
<tr>
<td>T/P ratio</td>
<td></td>
<td>1.70±0.09</td>
<td>1.30±0.003*</td>
</tr>
</tbody>
</table>

*Values given are mean±S.E. of the result obtained from four animals.

*Significantly (P<0.05) different as compared to the corresponding values after i/v administration of drug.