Pharmacokinetics of 17-hydroxyprogesterone Caproate, a Drug for Prevention of Preterm Delivery in Rats
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Purpose
17-hydroxyprogoesterone caproate (17-OHPC), the recommended treatment option to reduce the propensity towards preterm birth in high risk mothers, is given as a 250 mg weekly intramuscular injection of an oily formulation and shows beneficial effects in ~32% of the treated patients. Intramuscular administration is painful and inconvenient. It is important to evaluate potential alternate routes for this agent. The aim of the present study is to determine the pharmacokinetics of 17-OHPC in rats after various routes of administration.

Methods
Adult female SD rats were anaesthetized and catheters were placed in right jugular vein for serial blood sampling. 17-OHPC was solubilized in Cremophor: Ethanol mixture, and diluted with saline prior to injection. The rats were injected with a single (5 mg/kg) intravenous (n=4) or intramuscular (n=4) dose of 17-OHPC and periodic blood and cumulative urine samples were collected over 24 hr (IV) and 72 hr (IM). Plasma was separated and stored at -80oC until analysis. At the end of study the rats were euthanized; vital organs were collected for analysis. Plasma levels of 17-OHPC was analyzed using LC-MS/MS and pharmacokinetic parameters were obtained using non-compartmental analysis. The groups were compared using student t-test and p<0.05 was considered statistically significant.

Results
Intravenous injection of (5 mg/kg) 17-OHPC shows an early extensive distribution phase followed by elimination phase, whereas intramuscular injection shows an early absorption phase followed by elimination phase. The elimination rate constant was similar for 17-OHPC for both routes indicating that the drug was rapidly absorbed after IM injection. The t1/2 of 17-OHPC after IV injection was (~5.5 ± 4.3 hr) statistically not different from t1/2 after IM injection (8.9 ± 1.92 hr). AUC 0-∞, Clearance and Vd were similar after IV and IM routes. The bioavailability of 17-OHPC after IM injection was 100%.

Conclusion
IM injection in a solubilized dosage form leads to 100% bioavailability. Further studies are underway to determine bioavailability after PO dosing of the same solution and intramuscular injection of the oil formulation used in clinic.

<table>
<thead>
<tr>
<th>Route</th>
<th>t1/2 (hr)</th>
<th>tmax (hr)</th>
<th>AUC(0-∞) (mg/ml/hr)</th>
<th>Cl (L/hr)</th>
<th>Vd (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>0.21±0.35</td>
<td>2.4±0.75</td>
<td>1894+14.7</td>
<td>129±4.9</td>
<td>83±13.14</td>
</tr>
<tr>
<td>IM</td>
<td>0.8±0.35</td>
<td>8.9±1.92</td>
<td>2124±15.5</td>
<td>130±4.9</td>
<td>83±13.14</td>
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