Esmolol Population Pharmacokinetics in Critically-ill, Pediatric Patients

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RESULTS (continued)

Demographic Characteristics

<table>
<thead>
<tr>
<th>ETHIC</th>
<th>ESCAPE</th>
<th>COMBINED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 newborns: ≥28 days</td>
<td>14 child: ≥2 to 11y</td>
<td>50 newborns</td>
</tr>
<tr>
<td>41 infants: &gt;28 d to &lt;1y</td>
<td>13 adult: 12-16y</td>
<td>41 infants</td>
</tr>
<tr>
<td>52 child: ≥3 y to by</td>
<td></td>
<td>97 child/adultes</td>
</tr>
<tr>
<td>Weight(kg)</td>
<td>newborns: 3.6 (0.4)</td>
<td>infants: 14.9 (3.0)</td>
</tr>
<tr>
<td></td>
<td>48.9 (23.6)</td>
<td>25.2 (22)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic: 25 (17%)</td>
<td>non-Hispanic white: 50 (83%)</td>
<td>125 (20)</td>
</tr>
<tr>
<td>black: 9 (6%)</td>
<td>non-Hispanic black: 4 (12%)</td>
<td></td>
</tr>
<tr>
<td>Other: 2 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 (35%)</td>
<td>11 (41%)</td>
<td>61 (36%)</td>
</tr>
<tr>
<td>&lt; 65 (65%)</td>
<td>≥65 (15%)</td>
<td>≥109 (64%)</td>
</tr>
</tbody>
</table>

Esmolol Population Pharmacokinetics in Critically-ill, Pediatric Patients

INTRODUCTION

Esmolol Chemical Structure:

Basic Pharmacology
- β₁-selective antagonist
- very short duration of action
- administered for beta blockade of short duration

Adult Clinical Pharmacology
- Rapid control of ventricular rate in atrial fibrillation/flutter
- Noncompensatory sinus tachycardia
- Initial loading dose of 500 µg/kg
- Maintenance infusion of 50 - 200 µg/kg/min
- Ester linkage hydrolyzed rapidly by erythrocyte esterases
  - free acid metabolite and methanol
- No CYP dependent metabolism

Pediatric Trials with Esmolol
- ETHIC: Infants and Children Undergoing Treatment of Hypertension in After Surgical Repair of Coarctation of the Aorta
- ESCAPE: Pediatric Patients with Supraventricular Tachycardia
- Neither study designed for pop-PK
- Clinical settings different (OR vs Cath Lab) as well as clinical conduct
- ETHIC patients anesthetized

OBJECTIVES

1. To describe esmolol pharmacokinetics in pediatric patients via population-PK modeling
2. To identify covariate, demographic and clinical factors that are important predictors of variability in esmolol PK parameters

DESIGN / METHODS

- Combined data set contained 552 observations and included 4 dosing regimens (loading doses of 125, 250, 500 and 1000 µg/kg over 10 - 20 seconds and maintenance infusions of 125, 250, 300 and 500 µg/kg/min over 15 min)
- PK database was analyzed using nonlinear mixed-effects modeling with the NONMEM software, Version V, Level 1.1 (FO and FOCE Methods)
- The underlying structural model was a two compartment open model with two consecutive zero-order staged infusions as input

RESULTS

Baseline Model, Combined Dataset

Final Model, Combined Dataset

Final Model, Escape Dataset Only

RELEVANT MODEL RUNS

Model Description
- Base:
  - 2 CPM: fixed allometric on CL -7275.5 -675.8
  - 2 CPM: fixed allometric on CL and V -7321.2 -630.1
  - 2 CPM: fixed allometric on CL; CL-RAISE -7275.1 -0.4
  - 2 CPM: fixed allometric on CL; CL-SEX -7274.2 -1.1
  - 2 CPM: fixed allometric on CL; CL-AGE -7265.4 -10.1

REFERENCES

CONCLUSIONS
- The pediatric population PK model provided a robust description of esmolol PK across a wide range of ages (0.01 – 16.7 years) and body weights (2.6 – 114.1 kg).
- While 3 patients were found to influence model outcomes, there were no compelling reasons to remove them from the analysis.
- Model predictions were consistent with a linear, time-independent system.
- Newborns and infants appear to clear esmolol faster than children greater than 1 year of age. Clearance in children greater than 1 year of age is similar to that observed in adults.

BACKGROUND