Mechanistic Population Pharmacokinetics of Morphine in Neonates with Abstinence Syndrome after Oral Administration of Diluted Tincture of Opium

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Introduction

Neonatal Abstinence Syndrome (NAS) is a clinical syndrome of opiate withdrawal in neonates exposed to drugs prenatally via chronic maternal opiate use. Morphine is the standard first-line pharmacotherapy in NAS. However, the pharmacokinetic (PK) characteristics of morphine after oral administration in neonates is still unknown.

Objective

The aim of this analysis is to develop a morphine population pharmacokinetics (PopPK) model using data collected during a randomized control trial in infants with NAS.

Methods

The development of the PK model involved two major steps: 1) a structural model after intravenous administration in adults was extrapolated to pediatrics using the allometric scaling approach with maturation of PK parameters based on age; and 2) a population PK model after oral administration of diluted tincture of opium (DTO) was built based on this structural model and plasma data collected from the current clinical trial.

PopPK model analysis was performed using Phoenix NLME 1.3 (Pharsight, Cary, North Carolina). The first order conditional estimation method with interaction (FOCE-I) was used in the modeling process.

A three compartment structural model based on adult PK along with physiologic models for body weight and maturation was employed to analyze the sparse data from neonates. The maturation effect on clearance was modeled as a function of PMA and on volume as a function of PMA. In external evaluation of the structural IV model, the predictions are in good agreement with the observed PK profile in both adults and pediatrics (Figure 1).

88 plasma samples were collected from 34 neonates with abstinence syndrome after oral administration of DTO, in which morphine is the active ingredient. By fixing the PK parameters in the structural PK model after IV administration, the estimated first-order absorption rate constant was 0.751 hour⁻¹ and the bioavailability was 48.5% in neonates with abstinence syndrome (Table 1). Bayesian individual concentration time profiles during the entire study were simulated based on post hoc PK parameter estimates in four representative subjects (Figure 2).

Results

Table 1: Final Parameters Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Point Estimate</th>
<th>95% Confidence Interval</th>
<th>95% Percentile Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ka</td>
<td>1/hour</td>
<td>0.751</td>
<td>(0.196, 1.31)</td>
<td>0.732</td>
</tr>
<tr>
<td>F</td>
<td>%</td>
<td>48.5</td>
<td>(38.9, 58.2)</td>
<td>45.5</td>
</tr>
<tr>
<td>Vstd*</td>
<td>Liter</td>
<td>17.8</td>
<td>17.8</td>
<td></td>
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<tr>
<td>CLstd*</td>
<td>Liter/hour</td>
<td>75.3</td>
<td>75.3</td>
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<tr>
<td>Qstd*</td>
<td>Liter/hour</td>
<td>87.3</td>
<td>87.3</td>
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<tr>
<td>V3std*</td>
<td>Liter</td>
<td>199</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>CLmat50*</td>
<td>Liter/hour</td>
<td>58.3</td>
<td>58.3</td>
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</tr>
</tbody>
</table>

Conclusion

The population PK model of morphine after oral administration of DTO is reasonable and acceptable, and can be used to guide future studies by simulating exposure under different dosing regimens among various infants with NAS.

Reference