POPULATION PHARMACOKINETICS OF MILRINONE IN INFANTS AND CHILDREN

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A project of the Best Pharmaceuticals for Children Act
Disclosures

• Nothing to disclose
Milrinone is a PDE-3 inhibitor with inotropic and vasodilatory properties

• Pharmacokinetics (PK)
  • Highly protein bound (77 – 96%)
  • Volume of distribution approximately 30 – 60 L/70kg
  • 83% of drug eliminated unchanged in the urine
  • Risk of toxic drug accumulation with renal dysfunction

• Pharmacodynamics (PD)
  • Adult therapeutic plasma concentration range 100 – 300 ng/mL
  • In children, hemodynamic effect at peak concentration of 235 ng/mL

• Milrinone is not approved for use in children
  • Routinely used post cardiac surgery
  • Commonly used in heart failure conditions
Objective

- Develop a population pharmacokinetic (PopPK) model for milrinone in children ≤18 years of age
- Perform dose-exposure simulations to assess optimal milrinone dosing in children with variable renal function
Methods – POPS trial
Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care

<21 years of age receiving intravenous milrinone per standard of care

Excluded if: Known pregnancy

<sup>1</sup>NCT01431326
Methods – PK modeling

• 1-, 2-, and 3- compartment models evaluated
  • Nonlinear mixed effect modeling (NONMEM v.7.4)
  • Estimates of population PK parameters and inter-individual variability
• Covariate evaluation: gender, race, obesity, PMA and PNA, serum, ECMO, indication, surgery history, creatinine, creatinine clearance

• Milrinone dosing-exposure simulations
  • Surrogate PD target for efficacy: plasma concentration in the 100 – 300 ng/mL range
Results - 74 children contributed 111 PK samples

<table>
<thead>
<tr>
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<th>Median (range)*</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>2.9 (0.01, 18)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>13.1 (2.6-157.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>39 (53%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.5 (0.1-3.1)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73m2)</td>
<td>117.2 (13.1-261.3)</td>
</tr>
<tr>
<td>On ECMO, n (%)</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Infusion rate (mcg/kg/min)</td>
<td>0.5 (0.1-41)</td>
</tr>
<tr>
<td>PK samples per subject</td>
<td>2 (1 – 11)</td>
</tr>
</tbody>
</table>

*unless otherwise specified
Observed concentrations vs. time after last dose

All

First 500 hours
One – compartment population PK model

\[ TVCL = 16.7 \times \left(\frac{\text{weight}}{70}\right)^{1.05} \times \left(\frac{\text{Creatinine clearance}}{110}\right)^{0.6} \]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimate (RSE)</th>
<th>Bootstrap Median (5\textsuperscript{th}, 95\textsuperscript{th} percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL_{70kg}$ (L/h)</td>
<td>16.7 (14%)</td>
<td>16.6 (13.6, 21.8)</td>
</tr>
<tr>
<td>$V_{70kg}$ (L)</td>
<td>31.7 (30%)</td>
<td>32.8 (12.6, 134.6)</td>
</tr>
<tr>
<td>Power function for CrCL on CL</td>
<td>0.603 (22%)</td>
<td>0.61 (0.37, 0.85)</td>
</tr>
<tr>
<td>Allometric coefficient for weight on CL</td>
<td>1.05 (9%)</td>
<td>1.06 (0.9, 1.23)</td>
</tr>
<tr>
<td>IIV CL (CV%)</td>
<td>72 (26%)</td>
<td>70 (56, 85)</td>
</tr>
<tr>
<td>Residual proportional error (%)</td>
<td>32 (28%)</td>
<td>28 (19, 37)</td>
</tr>
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</table>

RSE: relative standard error (%); IIV: inter-individual variability
Relationship between milrinone elimination and estimated GFR

Graph showing the relationship between creatinine clearance (Schwartz) and individual milrinone clearance (L/hr/kg).

Box plots indicating milrinone half-life (hours) at different creatinine clearance ranges (CrCl): <31 ml/min/1.73m2, 31-60 ml/min/1.73m2, 61-120 ml/min/1.73m2, >120 ml/min/1.73m2.
Milrinone dose simulation in 3kg neonate

25 mcg/kg load followed by 0.25 mcg/kg/min infusion

50 mcg/kg load followed by 0.5 mcg/kg/min infusion
Milrinone dose simulation in 30kg child

25 mcg/kg load followed by 0.25 mcg/kg/min infusion

50 mcg/kg load followed by 0.5 mcg/kg/min infusion
Limitations

• Opportunistic design, sparse sampling

• Large inter-individual variability

• Safe exposure limits unknown

• No pharmacodynamic analysis
Conclusions

• Milrinone clearance increases with improvement in creatinine clearance

• ECMO was not a determinant of clearance, possibly because of sample size or changes in renal function

• 50 mcg/kg load & 0.5 mcg/kg/min infusion dosing is appropriate in the setting of normal creatinine clearance in neonates and children

• When creatinine clearance is severely impaired, 25 mcg/kg load & 0.25 mcg/kg/min infusion results in therapeutic exposures after ~5 hours of infusion
Acknowledgement

- We thank the principal investigators, research teams, and patients in their support of the POP01 study.

<table>
<thead>
<tr>
<th>Site PIs</th>
<th>City</th>
<th>State</th>
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</thead>
<tbody>
<tr>
<td>Mueller, William &amp; Yogev, Ram</td>
<td>Chicago</td>
<td>IL</td>
</tr>
<tr>
<td>Mourani, Peter</td>
<td>Aurora</td>
<td>CO</td>
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<td>Watt, Kevin</td>
<td>Durham</td>
<td>NC</td>
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<td>Sullivan, Janice</td>
<td>Louisville</td>
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<td>Atz, Andrew</td>
<td>Charleston</td>
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<td>Cleveland</td>
<td>OH</td>
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<tr>
<td>Al-Uzri, Amira</td>
<td>Portland</td>
<td>OR</td>
</tr>
<tr>
<td>Adu-Darko, Michelle</td>
<td>Charlottesville</td>
<td>VA</td>
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Additional slides
## Population PK of Milrinone in Children

<table>
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<tbody>
<tr>
<td>29 infants &lt;29 w GA; 0.52-1.29kg</td>
<td>235 children 0-&lt;6 years</td>
<td>20 children 3-22 months, 3.2-12 kg</td>
<td>19 children 0-&lt;=13yrs, 3.5-40kg</td>
</tr>
<tr>
<td>1-comp model</td>
<td>1-comp model</td>
<td>3-comp model</td>
<td>2-comp model</td>
</tr>
<tr>
<td>0.25-0.75mcg/kg/min</td>
<td>25/75 mcg/kg load then 0.25/0.75mcg/kg/min</td>
<td>50mcg/kg load then 0.5 mcg/kg/min</td>
<td>50mcg/kg load then 0.25-0.75 mcg/kg/min</td>
</tr>
<tr>
<td>Cl=0.64ml/kg/min = 2.7 L/hr/70kg</td>
<td>CL=2.42ml/kg/min*[1+0.0396*age] = 10 L/hr/70kg for 0yrs = 12 L/hr/70kg for 5 yrs</td>
<td>CL=2.5ml/kg/min*[1+0.058*age] CL2=14.5(1.7)*weight CL3=5(2.5)*weight</td>
<td>CL=5.67 ml/kg/min =23.8 L/hr/70kg</td>
</tr>
<tr>
<td>V=576ml/kg [21%] = 40 L/70kg</td>
<td>V=482 ml/kg = 33.7 L/70kg</td>
<td>Vss=871 ml/kg = 61 L/70kg</td>
<td>Vss=830ml/kg =58.1 L/70kg</td>
</tr>
<tr>
<td>Allometrically scaled weight on CL and V</td>
<td>Weight &amp; age linear on CL Weight linear on V</td>
<td>Weight linear for all Weight &amp;age linear on CL</td>
<td>Weight linear for all</td>
</tr>
</tbody>
</table>

Age distribution by ECMO

Graphs by ECMO
Observed concentrations vs. time after last dose

All

First 500 hours
Observed concentrations vs. time after end of last dose

All

First 5 hours
Population PK model equations

- TVCL = \text{THETA}(1) \times ((\text{WT}/70)^{\text{THETA}(4)}) \times (\text{NEWCRCL}/110)^{\text{THETA}(3)}
- CL = TVCL \times \exp(\text{ETA}(1))
- TVV = \text{THETA}(2) \times (\text{WT}/70)
- V = TVV \times \exp(\text{ETA}(2))
Diagnostic plots

- Observed Concentration vs. Population Predictions
- Observed Concentration vs. Individual Predictions
- Conditional Weighted Residuals vs. Time After First Dose
- Conditional Weighted Residuals vs. Population Predictions
Milrinone half-life by age group
Milrinone dose simulation in 13 kg child

- 25 mcg/kg load followed by 0.25 mcg/kg/min infusion
- 50 mcg/kg load followed by 0.5 mcg/kg/min infusion
Milrinone dose simulation in 70 kg child

25 mcg/kg load followed by 0.25 mcg/kg/min infusion

50 mcg/kg load followed by 0.5 mcg/kg/min infusion
Modified Schwartz Equation

• \[ crcl = \frac{htcm \times 0.45}{scr} \text{if} \ pnapkwk \geq 1 \ & \ pnapkwk \leq 52 \ & \ gaw \geq 37 \ & \ gaw \neq . \]

• \[ crcl = \frac{htcm \times 0.33}{scr} \text{if} \ pnapkwk \leq 52 \ & \ gaw < 37 \ & \ gaw \neq . \]

• \[ crcl = \frac{htcm \times 0.55}{scr} \text{if} \ pnapkyr \geq 13 \ & \ pnapkyr \leq 13 \ & \ crcl = . \]

• \[ crcl = \frac{htcm \times 0.7}{scr} \text{if} \ pnapkyr > 13 \ & \ pnapkyr \leq 18 \ & \ sex = 2 \ & \ crcl = . \]

• \[ crcl = \frac{htcm \times 0.7}{scr} \text{if} \ pnapkyr > 13 \ & \ pnapkyr \leq 18 \ & \ sex = 1 \ & \ crcl = . \]
Visual Predictive Check

7% of observations outside the 90% prediction interval
Milrinone dose simulation in 30kg child

25 mcg/kg load followed by 0.25 mcg/kg/min infusion

50 mcg/kg load followed by 0.5 mcg/kg/min infusion