Background

- Cardiac surgery associated acute kidney injury (CS-AKI) occurs in 30-40% of children
- Serum creatinine (SCR) is a delayed marker of CS-AKI, resulting in challenges in medication dose adjustments.
- Milrinone is prescribed to provide afterload reduction and lusitropy in children after cardiac surgery
- The purpose of this study was to evaluate milrinone pharmacokinetics (PK) in critically ill infants < 1 year who underwent cardiac surgery. We aimed to determine the relationship between PK parameters and biomarkers of kidney injury

Methods

- Prospective multicenter observational study
- Baseline SCr and urinary CS-AKI biomarkers (NGAL, FABP, IL-18 and KIM-1) were obtained pre-operatively and sequentially for 24 hours
- Peak biomarker concentration was used for analyses
- Milrinone concentrations were obtained at specific time points following the initiation of cardiac bypass
- Non-compartmental analysis was performed using Phoenix V6.3 WinNonlin
- Univariate and multivariate regression analyses were used to evaluate the relationship between PK parameters and CS-AKI biomarkers

Results

Table 1. Pharmacokinetic parameters of milrinone in critically ill children undergoing cardiac surgery (L = liters, h = hours, µg = micrograms)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h)</td>
<td>0.0004 ± 0.0002</td>
<td>0.0006 ± 0.001</td>
</tr>
<tr>
<td>Volume of Distribution (L)</td>
<td>7261.02 ± 7.559.1</td>
<td>4391</td>
</tr>
<tr>
<td>Area under the curve (µg*h/L)</td>
<td>2644 – 9705.4</td>
<td>1.45 – 3.47</td>
</tr>
<tr>
<td>Half Life (h)</td>
<td>3.4 ± 5.23</td>
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</tr>
</tbody>
</table>

- There was no significant relationship between KIM-1 or IL-18 and half-life or clearance, respectively
- The combination of peak SCr and age significantly predicted clearance ($R^2 = 23\%$, $p = 0.018$) ($Cl = 0.0001598 + 1.367E-06\times(Age)$)

Implications

- Since the clearance of milrinone significantly tracked with SCr via regression analyses, dose adjustment based on kidney function may contribute to better precision in achieving targeted concentrations
- Novel CS-AKI biomarkers, including KIM-1, detect kidney injury in advance of a rise in SCr and have the potential for earlier attainment of milrinone therapeutic targets

Conclusions

- Early results suggest that CS-AKI biomarkers (specifically KIM-1) when combined with peak SCr may be useful in predicting milrinone half-life in infants undergoing cardiac surgery and has the potential to be used for clinical management
- The addition of age (an ontological maturation marker) to biomarkers may increase the prediction of PK parameters.
- Evaluation of other biomarkers, including NGAL, L-FABP and IL-18 will help to discriminate the selected combinations of markers that enhance milrinone therapy precision

Disclosures

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