Dosing of Antimicrobials in the Neonatal Intensive Care Unit: Does Clinical Practice Reflect Published Recommendations?

Morgan England
The University of Texas at Austin

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Disclosures

• I have documented no financial relationships to disclose or conflicts of interest to resolve.
• I have documented that this presentation involves discussion of off-label use of meropenem and fluconazole in infants.
Background

• Correct dosing in the NICU is important to avoid treatment failure and to prevent adverse events
• Neonatologists often use data extrapolated from adults and older children to guide drug dosing for infants
• Recent pharmacokinetics (PK) studies performed in infants provided optimized dosing recommendations for
  – Meropenem (2011)
  – Fluconazole loading dose (2011)
  – Fluconazole daily dose (2009)
• Whether these findings resulted in more appropriate dosing is unknown

Smith PB, PIDJ, 2011
Wade KC, PIDJ, 2009
Piper L, PIDJ, 2011
Objective

• Describe changes in dosing for meropenem and fluconazole in the NICU after publication of drug pharmacokinetics in infants
Methods

• Cohort study using an electronic health records from 362 NICUs managed by the Pediatrix Medical Group between 1997-2013

• Inclusion criteria
  – Received meropenem or fluconazole
  – <90 days postnatal age (PNA) at start of drug course

• Exclusion criteria
  – Dosing unavailable
  – Dosing consistent with prophylactic administration
    • Fluconazole courses that started before day of life 5, lasted >7 days, and began prior to any positive fungal culture
    • Courses dosed less frequently than every 24 hours
Methods

- **Definition:** “appropriate dosing”
  - Dose between 80% - 120% of the published recommendation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meropenem</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;32 weeks GA and &lt;14 days PNA</td>
<td>40 mg/kg/day</td>
</tr>
<tr>
<td>&lt;32 weeks GA and ≥14 days PNA</td>
<td>60 mg/kg/day</td>
</tr>
<tr>
<td>≥32 weeks GA and &lt;14 days PNA</td>
<td>60 mg/kg/day</td>
</tr>
<tr>
<td>≥32 weeks GA and ≥14 days PNA</td>
<td>90 mg/kg/day</td>
</tr>
<tr>
<td><strong>Fluconazole, loading dose</strong></td>
<td>25 mg/kg/day</td>
</tr>
<tr>
<td><strong>Fluconazole, daily dose</strong></td>
<td>12 mg/kg/day</td>
</tr>
</tbody>
</table>
Methods

• Calculated the proportion of appropriately dosed courses
  – Overall
  – By discharge year

• Evaluated the change in appropriate dosing over time
  – Linear regression to predict proportion of appropriately dosed courses using discharge year
  – Chi-square statistic to test for linear trend
## Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Courses n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meropenem (N=784 courses)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;32 weeks GA and &lt;14 days PNA</td>
<td>146 (19)</td>
</tr>
<tr>
<td>&lt;32 weeks GA and ≥14 days PNA</td>
<td>441 (56)</td>
</tr>
<tr>
<td>≥32 weeks GA and &lt;14 days PNA</td>
<td>112 (14)</td>
</tr>
<tr>
<td>≥32 weeks GA and ≥14 days PNA</td>
<td>85 (11)</td>
</tr>
<tr>
<td><strong>Fluconazole (N=805 courses)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;32 weeks GA and &lt;14 days PNA</td>
<td>174 (22)</td>
</tr>
<tr>
<td>&lt;32 weeks GA and ≥14 days PNA</td>
<td>406 (50)</td>
</tr>
<tr>
<td>≥32 weeks GA and &lt;14 days PNA</td>
<td>56 (7)</td>
</tr>
<tr>
<td>≥32 weeks GA and ≥14 days PNA</td>
<td>169 (21)</td>
</tr>
</tbody>
</table>
Courses Dosed Appropriately

Percentage Appropriately Dosed

- Meropenem: 20%
- Fluconazole, loading dose: 0%
- Fluconazole, daily dose: 10%
Of Inappropriate Doses, Percentage Underdosed

<table>
<thead>
<tr>
<th></th>
<th>Percentage Underdosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>70%</td>
</tr>
<tr>
<td>Fluconazole, loading dose</td>
<td>100%</td>
</tr>
<tr>
<td>Fluconazole, daily dose</td>
<td>100%</td>
</tr>
</tbody>
</table>
Meropenem

1.3% increase in correct doses per year ($P < 0.001$)
0.9% increase in correct doses per year (P < 0.001)
Fluconazole Daily Dose

1.2% increase in correct doses per year ($P < 0.001$)
Conclusion

- Majority of infants in the NICU do not receive the recommended doses of meropenem or fluconazole (loading dose or daily dose)
- Publication of PK results was associated with more appropriate dosing
Limitations

- Appropriate dose adjustments for renal function not considered
- Data not monitored for accuracy
- Abstracts presented 1 year prior to publications
- Possible misidentification of fluconazole prophylaxis
Future Studies

• Evaluate how antimicrobial dosing impacts safety and efficacy

• Quality improvement programs to improve accurate dosing through:
  – Increased education
  – Computerized order entry dosing guidelines
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