Pantoprazole Pharmacokinetics in Obese Children and Adolescents: Where Genes and Size Collide

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Disclosures

Funding
- Pediatric/Developmental Clinical Pharmacology training grant (T32HD069038-01; G.L. Kearns) and the Pediatric Trials Network (HHSN275201000003I; D.K. Benjamin, Jr.), both supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Bethesda, MD USA)
- Marion Merrell Dow Foundation Clinical Scholar grant (V. Shakhnovich and C. Friesen; co-PIs) from Children’s Mercy Kansas City, MO USA

Study Drug
- Thank you to Dr. Anil Modak and Cambridge Isotopes Laboratories (Andover, MA USA) for kindly providing the study drug

Childhood Obesity in the US

Obesity in Pediatrics

• Obese: BMI ≥ 95%
• Overweight: BMI ≥ 85% but ≤ 95%
• No guidance regarding dose-selection in overweight and obese children

Dosing Dilemma

Obesity-related Comorbidities
**Obesity-related Changes in Physiology**

- ↑ Body fat
- ↓ Lean body mass
- ↓ Basal metabolic rate
- ↑ Cardiac output
- ↑ Liver blood flow
- ↑ GFR

**The Proton Pump**

- Pantoprazole
- Omeprazole
- Lansoprazole
- Esomeprazole
- Rabeprazole
- Dexlansoprazole

**CYP2C19 Pharmacogenetics**

- CYP2C19 genetic variability
  - Alleles
    - *1 wild-type (“normal”)
    - *17 gain of function
    - *2 loss of function
  - Genotype-phenotype relationship
**Purpose of Study**

- Explore pharmacokinetic differences in Pantoprazole in overweight/obese vs. normal-weight children
- CYP2C19 activity

**Prospective PK Study**

- Genotype
- Single oral dose 1.2mg/LBW kg pantoprazole
- Plasma samples at 10 time-points

52 GERD patients (6-17yo)
- 26 Normal-weight (BMI 10-84th)
- 26 Overweight/Obese (BMI ≥ 85th)

**Methodology**

- TaqMan for CYP2C19 *17, *2, *3, *4
- Pantoprazole & CYP2C19 metabolites measured via HPLC-UV
- Plasma data analyzed via non-compartmental approach (Kinetica 5.0)
Results

• PK parameters in normal-weight vs. overweight/obese children
• Adjusted dose-for-weight

![AUC\text{tot} vs. BMI](image)

\[ r^2 = 0.4 \quad p < 0.01 \]

### PK in Overweight/Obese vs. Normal Weight Children

<table>
<thead>
<tr>
<th>PK Parameter (mean ± SD)</th>
<th>Normal Weight (n = 26)</th>
<th>Overweight/Obese (n = 26)</th>
<th>p-value (α = 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L_z ) (L/hr)</td>
<td>0.90 ± 0.25</td>
<td>0.79 ± 0.27</td>
<td>0.15</td>
</tr>
<tr>
<td>( CL/F ) (L/hr/kg)</td>
<td>0.43 ± 0.22</td>
<td>0.29 ± 0.17</td>
<td>0.05</td>
</tr>
<tr>
<td>( V_{Dss}/F ) (L/kg)</td>
<td>0.61 ± 0.31</td>
<td>0.47 ± 0.33</td>
<td>0.19</td>
</tr>
<tr>
<td>( AUC_{tot} ) (mg/L per 1 mg/kg dose)</td>
<td>3.83 ± 2.68</td>
<td>4.24 ± 2.75</td>
<td>0.80</td>
</tr>
</tbody>
</table>
Conclusions

- CYP2C19 genotype appears a primary determinant of pantoprazole PK
- Obesity may be an important source of individual variability in pantoprazole PK
- CYP2C19 activity score may be clinically helpful
Future Directions: CYP2C19 Activity Score

- Each allele designated a number
  - *1*1 = 1.0

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2, *3, *4</td>
<td>(0)</td>
</tr>
<tr>
<td>*1</td>
<td>(0.5)</td>
</tr>
<tr>
<td>*17</td>
<td>(1)</td>
</tr>
</tbody>
</table>

Pediatric CYP2C19 Activity Score

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<td>*1</td>
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<tr>
<td>*17</td>
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</tbody>
</table>

Thank you

- Gregory L. Kearns, PharmD, PhD
- Susan Abdel-Rahman, PharmD
- Craig Friesen, MD
- Jaylene Weigel, RN, CCRC
- J. Steven Leeder, PharmD, PhD
- Robin Pearce, PhD
- Andrea Gaedigk, PhD
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CYP2C19 Metabolism of PPIs

Figure 1. CYP2C19 Genotype-Phenotype Relationship for Pantoprazole and Omeprazole


Obesity Epidemic in Children

Prevalence of Childhood Overweight (including obesity) 2000 to date

Pantoprazole Exposure

*p<0.0001

*p<0.01