

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

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Disclosures

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Study Drug

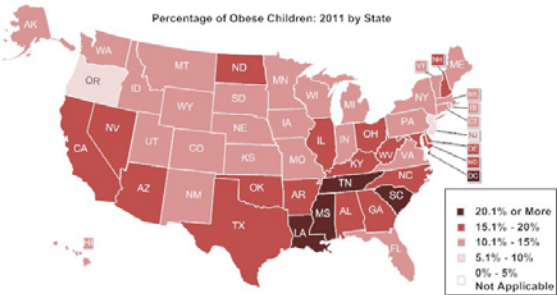
- Thank you to Dr. Anil Modak and Cambridge Isotopes Laboratories (Andover, MA USA) for kindly providing the study drug



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Childhood Obesity in the US



<http://www.ncsl.org/research/health/childhood-obesity-trends-state-rates.aspx>
last accessed May 6, 2015

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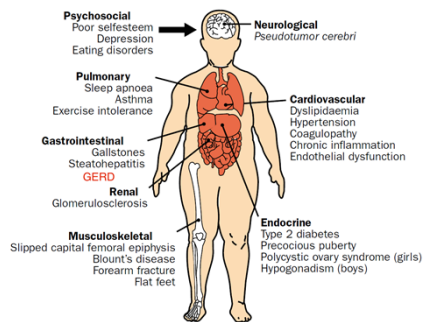
Obesity in Pediatrics

- Obese: BMI \geq 95%
- Overweight: BMI \geq 85% but \leq 95%
- No guidance regarding dose-selection in overweight and obese children

Dosing Dilemma



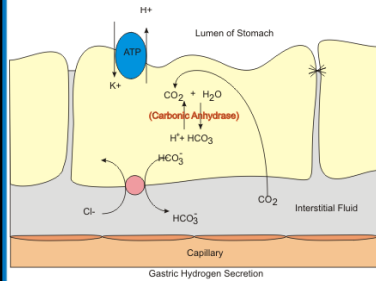
Obesity-related Comorbidities



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

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Prospective PK Study

52 GERD patients
(6-17yo)

26 Normal-weight
(BMI 10-84th)

26 Overweight/Obese
(BMI ≥ 85th)

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

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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)

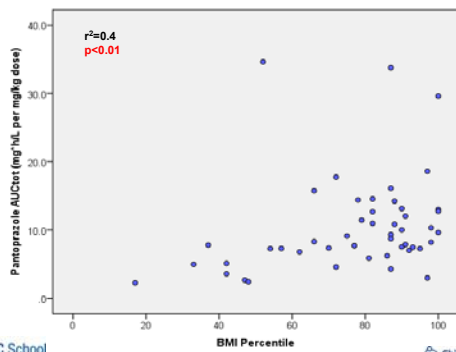
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Results

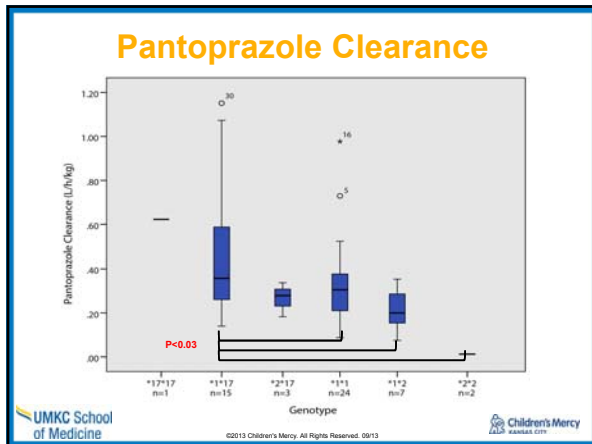
- PK parameters in normal-weight vs. overweight/obese children
- Adjusted dose-for-weight

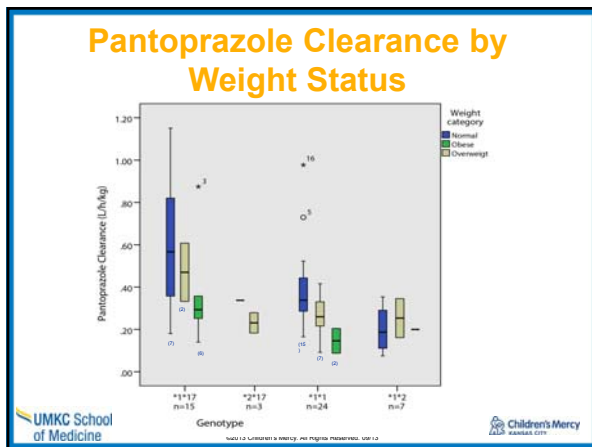
AUC_{tot} vs. BMI



PK in Overweight/Obese vs. Normal Weight Children

PK Parameter (mean ± SD)	Normal Weight (n = 26)	Overweight/obese (n = 26)	p-value (α = 0.05)
Lz (1/hr)	0.90 ± 0.25	0.79 ± 0.27	0.15
CL/F (L/hr/kg)	0.43 ± 0.23	0.29 ± 0.17	0.05
VDss/F (L/kg)	0.61 ± 0.31	0.47 ± 0.33	0.19
AUC _{tot} (mg/L*hr per 1 mg/kg dose)	3.83 ± 2.66	4.24 ± 2.75	0.60







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



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Future Directions: CYP2C19 Activity Score

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

	*2, *3, *4	(0)
N	*1	(0.5)
	*17	(1)

Pediatric CYP2C19 Activity Score

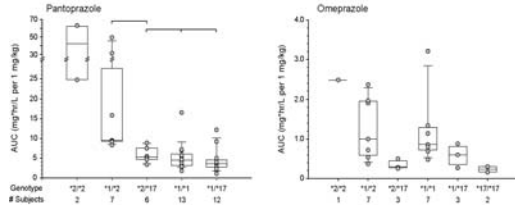
	*2, *3, *4
N	*1
	*17

Thank you

- | | |
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| <ul style="list-style-type: none"> • Gregory L. Kearns, PharmD, PhD • Susan Abdel-Rahman, PharmD • Craig Friesen, MD • Jaylene Weigel, RN, CCRC | <ul style="list-style-type: none"> • J. Steven Leeder, PharmD, PhD • Robin Pearce, PhD • Andrea Gaedigk, PhD • Mandy Riffel • Annie Frerking • Joshua Wirtz |
|---|---|

CYP2C19 Metabolism of PPIs

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



Kearns GL, Leader JS, Gaedigk A. Impact of the CYP2C19*17 allele on the pharmacokinetics of omeprazole and pantoprazole in children: evidence for a differential effect. *Drug Metab Dispos* 2010;38:894-897.

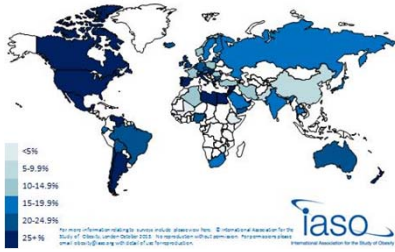


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Obesity Epidemic in Children

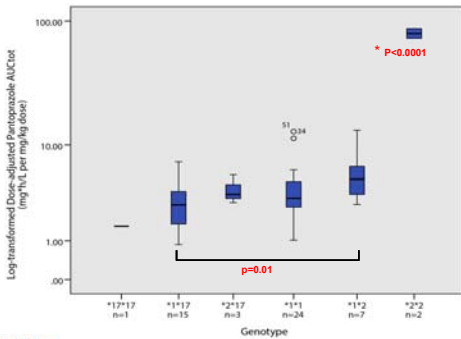
Prevalence of Childhood Overweight (including obesity) 2000 to date



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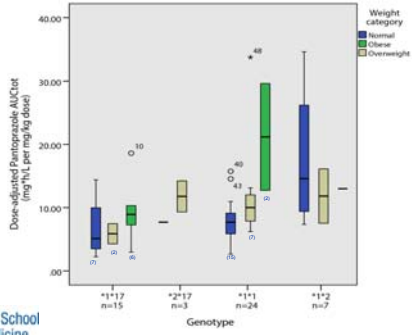
Pantoprazole Exposure



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Pantoprazole Exposure by Weight Status



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