Rifapentine Pharmacokinetics in Children Receiving Once Weekly Rifapentine and Isoniazid for the Treatment of Latent Tuberculosis Infection

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Background

- Children with LTBI have a high risk of progressing to severe disease
- The CDC recently recommended as alternate treatment for adults with LTBI, 12 once-weekly doses of RPT + INH, based on a Phase 3 RCT in 8,053 patients (NEJM 2011)
- In this treatment trial, RPT mg/kg dosages in children were higher than adults, because prior PK data in younger children demonstrated lower RPT AUC than was anticipated from studies in adults
- In the PK substudy of the Phase 3 treatment trial, we compared RPT AUC between children and adults

Methods

- 80 children (2 to 11 years) and 77 adults (> 18 years) were evaluated in the PK substudy
- Children received RPT doses (300 to 900 mg) adjusted by weight and adults received 900 mg doses
- Children who could not swallow whole tablets were given crushed drug mixed in simple oral suspensions
- The sparse sampling design used a sample drawn after at least 3-weeks of treatment, and collected 24-hours after administration of drugs
- Nonlinear, mixed effects regression models were developed with historical PK data from children and adults (intensive sampling after once-weekly RPT treatments) followed by joint analysis of all data

Demographic and clinical data in the 157 patients with LTBI

	Children	Adults	*P-value**
Number subjects	**80**	**77**	
Age, median (range)	**4.5 (2-11)**	**40 (19-63)**	**<.001**
Race			.50
Black, n (%)	11 (14)	16 (21)	
White, n (%)	65 (81)	57 (74)	
Asian, n (%)	4 (5)	4 (5)	
Ethnicity, Hispanic	68 (85)	54 (70)	.03
Gender, male, n (%)	41 (51)	40 (52)	.93
HIV infection, n (%)	**0/5**	**1/54 (2)**	
Drug administration with food, n (%)	**70 (88)**	**53 (69)**	**.005**
Drug administration by whole tablets, n (%)	**25 (31)**	**77 (100)**	**<.001**
**P*-value by Chi-square or Mann-Whitney Rank			

RPT dosage was greater in children vs. adults $AUC_{0\text{-}inf}$ was greater in children vs. adults, and in children with whole vs. crushed tablets

	Children			**Adults**
	All children n=80	Whole tablet n=25	Crushed tablet n=55	n=77
Dosage, mg/kg, Geometric mean (90% CI)	22.6 (21.6-23.5)	21.2 (19.7-22.9)	23.2 (22.0-24.4)	10.7 (10.3-11.2)
Dosage, vs. adults, Ratio geometric mean	2.10 * (1.98-2.23)	1.98 * (1.81-2.16)	2.16 * (2.02-2.31)	
$AUC_{0\text{-}inf}$, mcg*h/mL, Geometric mean (90% CI)	650 (603-701)	809 (710-921)	588 (539-642)	483 (450-518)
$AUC_{0\text{-}inf}$, vs. adults, Ratio geometric mean	1.35 * (1.21-1.49)	1.68* (1.45-1.93)	1.22** (1.09-1.36)	

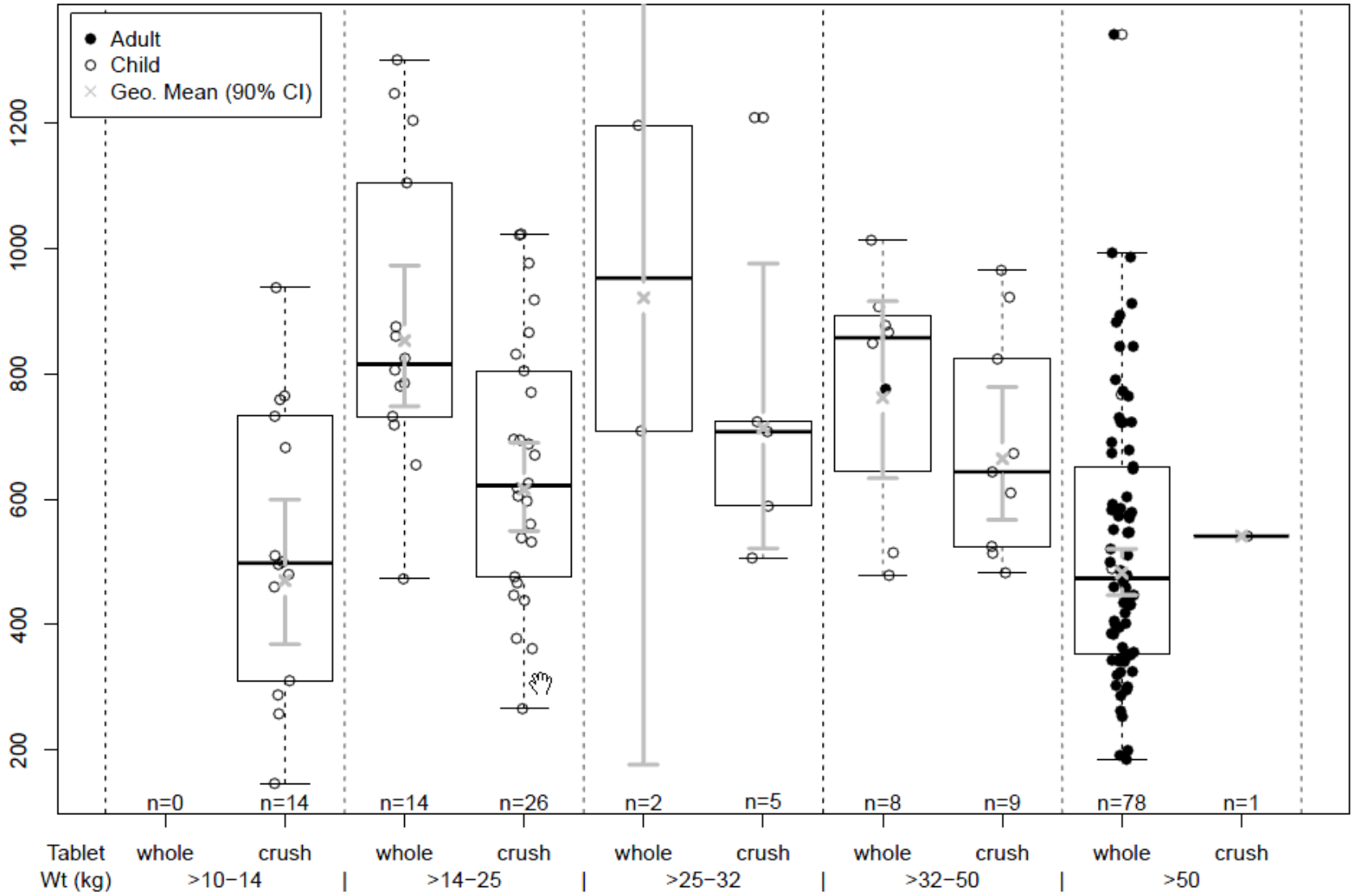
* P-value< .0001; ** P <.01

Factors in the mixed model ANOVA, n = 157	Sample size	$AUC_{0\text{-inf}}$, mcg*h/mL, adjusted mean*	*P*-value for groups**
Group effect			*P* = 0.016
1-Child - Crushed	55	524	.006 1 vs. 2
2-Child - Whole	25	679	.95 1 vs. 3
3-Adult - Whole	77	530	.19 2 vs. 3
			.71 3 vs.1&2
Food effect			*P* < 0.0001
Food	123	659	
Fasting	34	498	
Dose effect (weight band, dosage range)			*P* = 0.04
1 - 300 (11-14 kg, 21-27mg/kg)	13	459	.75 1 vs. 5
2 - 450 (14-27 kg,17-32mg/kg)	41	626	.21 2 vs. 5
3 - 600 (25-63 kg,10-24mg/kg)	7	699	.13 3 vs. 5
4 - 750 (31-49 kg,15-24mg/kg)	17	626	.20 4 vs. 5
5 - 900 (53-169 kg, 5-17mg/kg)	79	493	Group 5

*RPT AUC by ANOVA of ln data adjusted for other sign. factors and back transformed to the original scale.

***P*-value by Fisher's Least Significant Difference for pairwise comparisons of groups and contrast t-test for adults vs. all children.

Variability of RPT $AUC_{0\text{-}inf}$ was substantial



Summary

- Compared to adults, RPT GM dosage (mg/kg) was 110% higher and $AUC_{0\text{-inf}}$ 35% greater in children
- RPT $AUC_{0\text{-inf}}$ was lower in subjects taking crushed versus whole tablets
- Study drugs were clinically well tolerated in both children and adults
- There was substantial variability of RPT $AUC_{0\text{-inf}}$
- A significant food effect was found