Population pharmacokinetics of benznidazole in a cohort of children under 12 years old with Chagas disease

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Background

Chagas disease, caused by the parasite Trypanosoma cruzi, can lead to long term cardiac morbidity. Treatment of children with benznidazole (BNZ) is effective, but no pediatric pharmacokinetics data are available and clinical pharmacology information on the drug is scarce. No information is available for children under 2 years of age.

Methods

Prospective population pharmacokinetics (PopPK) cohort study in children 0-12 years old with Chagas disease between 2011 and 2012 at 5 recruitment centers in Argentina (PEDCHAGAS Network) (clinicaltrials.gov #NCT01549236). Patients were treated with BNZ (Lafepe, Brazil) 12.5 or 100 mg tablets, dose: 5-8 mg/kg/d bid p.o. for 60 days. Treatment response was evaluated by *T. cruzi* specific PCRq, and anti-*T cruzi* antibody titers. Five blood samples per child were obtained on Whatman 903 paper for BNZ measurements by HPLC-MS/MS. BNZ data was modelled using NONMEM (version 7.2) .

Results

81 were enrolled (2 screening failures). Seventy-six (76) patients completed treatment, and 5 discontinued. Median patient age was 12 months (IQR 6-72m). 47 (58%) patients were girls. 44 patients were administered the pediatric (i.e. 12.5 mg tablets) formulation. Five patients discontinued treatment, 3 due to adverse drug reactions, and 2 due to lack of adherence. A total of 387 blood BNZ measurements were obtained. Median observed Cmax was 8.32 mg/L (IQR 5.95–11.8). Median trough concentrations was 2 mg/L (IQR 1.25–3.77). Observed Cmax were higher in children treated with the 100 mg tablet, compared to the children treated with the 12.5 mg tablet (median 10.48 mg/L and 6.8 mg/L, respectively. Mann Whitney test, p<0.001). Trough levels were also higher in children treated with 100 mg tablets, compared to 12.5 mg tablets (median 3.36 vs 1.58 mg/L, Mann Whitney test p<0.001).

Population Pharmacokinetics Modeling and Simulation: 1-compartment model best fit the data. The results of the 1 compartment model with oral absorption are described in Table 1. Model diagnostic plots suggest adequate fit of the model to the data (Figures 1 & 2).

Covariate modeling: Covariate analysis suggested a significant influence of weight on volume of distribution and on clearance of BNZ. Addition of weight to the model decreased the objective function suggesting a statistically significant effect of weight on both parameters. Age seemed to also have an influence on both parameters, but this effect disappeared when weight was included in the model, likely reflecting the strong covariance between age and weight in children. None of the remaining covariates (dose per kg, total daily dose of BNZ, centre where patient was enrolled and treated, gender, tablet form -12.5 or 100 mg-) had a significant effect on the model parameters, and were not included in the final model.

The final model included a direct relationship of weight on volume of distribution, and an allometric (exponential) relationship of weight on clearance. Final parameter estimates can be found in Table 2.

Final parameter estimates were as follows:

$$V/F = 1.73 + 0.79 \times Weight\ (kg)$$

$$CL/F = 0.05 + 1.98 \times (Weight\ (kg) / 70)^{0.75}$$

Absolute Clearance (CL/F) showed a strong correlation with Age (Figure), increasing quickly during the first months of life, and a CL/F similar to that reported in adults approximately after 10 years of age (Figure 3). However, when CL/F is expressed as a function of weight (i.e. CL/F/WT), weight-corrected CL/F showed a significant decrease with age (Figure 4), reaching previously reported adult levels approximately around 8-10 years of age.

Overall median estimated Css (assuming a 7 mg/kg/d BNZ dose) was 6 mg/L (95% CI 5.25-6.58).

Age-stratified Css are summarized in Table 6. Groups are statistically significantly different among each other (Anova, p<0.05). Increase in Css with age can be easily observed in Figure 5 and table 3.

Discussion

Observed benznidazole plasma concentrations in children, and particularly in infants, were markedly lower than those previously reported in adults (treated with comparable mg/kg doses), but nevertheless associated to a high therapeutic response in our cohort.

Unlike adults, children have few adverse reactions to the drug, suggesting that there may be a correlation between drug concentrations and ADRs. Our results suggest that studies with lower doses in adults may be important.

PEDCHAGAS Network Centers
01 - Hospital de Niños Ricardo Gutiérrez de Buenos Aires
02 - Hospital de Niños Doctor Hector Quintana de Jujuy
03 - Hospital Público Materno Infantil de Salta
04 - Centro de Chagas y Patología Regional de Santiago del Estero
05 - Instituto Nacional de Parasitología Dr. Mario Fatala Chaben

Table 1. PedChagas Network

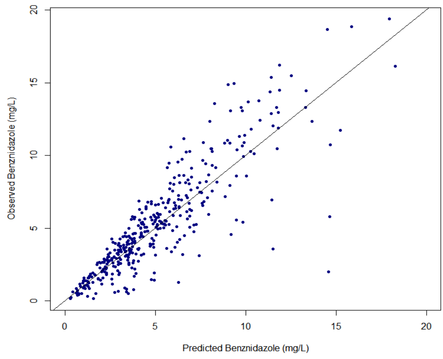

Figure 1. Goodness-of-fit (GOF) plot, 1 compartment model with oral absorption, no covariates

Parameter	Median [95%CI]	Interindividual variability [95%CI]
Ka (hr^{-1})	0.747 [0.28-1.87]	70.7% [40.7-102.8%]
V/F (L)	10.8 [6.65-14.59]	78.4% [62.3-89.4%]
CL/F (L/hr)	0.59 [0.52-0.67]	61.6% [50.9-70.7%]
Residual error (Proportional)	36.8% [32.1-40.7%]	

Table 1. BNZ PopPK parameters. One compartment model with oral absorption, proportional error model, no covariates.

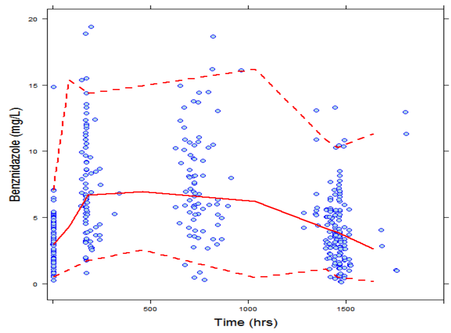

Figure 2. Visual Predicted Check (VPC) plot, 1 compartment model with oral absorption, no covariates

Parameter	Median [95% CI]	Interindividual variability [95% CI]
Ka (h^{-1})	1.09 [0.75;1.75]	36.2% [26.9; 58.4%]
V/F (L) b0+b1 x WT	b0 = 1.73 [0.02; 4.18] b1 = 0.79 [0.58; 0.99]	46.4% [27.7;61.6%]
CL/F (L/hr) b0 + b1 x (WT/70)^b2	b0 = 0.05 [0; 0.29] b1 =1.98 [1.64; 2.97] b2 = 0.75 [0.45; 1.51]	36.8% [26.5; 61.4%]
Residual error (Proportional)	38% [33.8; 42.6%]	

Table 2. Final parameter estimates, with covariates

Age	<2 months old	2m - 1 year old	1y - 7 years old	7y- -12 years old
Css (mg/L) (Median [95% CI])	4.13 [3.68-4.81]	4.61 [3.72-6.39]	5.91 [5.25-6.75]	8.69 [7.86-9.17]
AUC (mgxhr/L)	48.61 [44.17-57.71]	55.37 [44.69-76.72]	70.85 [63.04-81.6]	104.30 [94.3-110.1]

Table 3. Estimated Css by age group

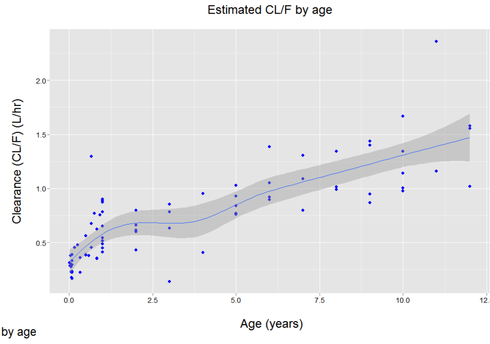

Figure 3. Clearance (CL/F) vs Age (years). CL/F increases rapidly during the first year of life, and reaches the reported adult level approximately at 10 years of age

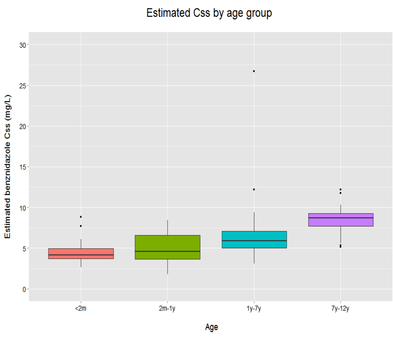

Figure 5. Boxplot estimated Css vs age group (simulated dose: 7mg/kg/day)

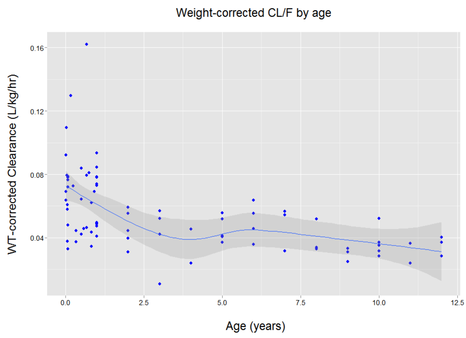

Figure 4. Weight-corrected CL/F, showing decrease with age

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