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A new paediatric tablet strength of benznidazole for the treatment of Chagas disease

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BACKGROUND

- Control programs efforts in the 1990s in the Southern Cone have reduced vector-borne transmission of *T. cruzi*. Non-vector-borne infections such as oral, blood transfusion and congenital transmission have received increased attention.
- Most infections and treatments for the acute and early chronic phase of the infection involve children. In particular, treatment of congenital Chagas infections in newborn infants and school-aged children diagnosed via school-screening surveys has become an increasingly important control issue.

Benznidazole, the main drug to treat acute Chagas, is only available as a tablet strength of 100mg.

Children below 20 kg are treated with fractions of these tablets.

Figure 1: Benznidazole tablet fractionation in a health centre in Honduras

- Current dosing regimens for children (weight-based benznidazole twice a day for 30–60 days) are extrapolated from adult patient data and empirically derived from clinical experience.
- Weight-based dosing regimens often represent a range around a specified dose.
- Variation in dosing occurs from fractionation of scored tablets and use of extemporaneous formulations, which adds further variation and imprecision in drug dosing[1].
- To respond to the urgent need for a paediatric formulation for Chagas disease, the Drugs for Neglected Diseases *initiative* (DND*i*, Switzerland) and the Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE, Brazil) have joined efforts to address this gap.
- We reviewed the available dose recommendations and treatment data from various groups working with infants/children with Chagas disease to determine a paediatric tablet strength that could best complement the current 100mg tablet.

METHODOLOGY

The following steps were used to determine the appropriate paediatric tablet strength and formulation:

- **Verification of target paediatric therapeutic dose range for benznidazol:** review of available paediatric dose recommendations for benznidazole in WHO guidelines, national control programs, and textbooks.
- **Review of paediatric dosing practices from endemic regions in Latin America:** review of treatment data from different treatment centres in Latin America to confirm the weight and treatment dose range.
- **Comparison of target dose recommendations against the therapeutic dose range used in practice by a group of clinical experts:** this evaluation was done to confirm the therapeutic dose range used for the new paediatric benznidazole across age and weight ranges of interest.
- **Assessment of formulation and regimen characteristics:** clinical experts in Chagas control programs discussed the required regimen characteristics, such as drug formulations (ie, liquid solutions, dispersible tablets), need and acceptability of the use of tablet fractions, and other options, to determine the paediatric tablet strength.
- **Ethics clearance:** Not applicable. Secondary analyses were done on anonymized data.

RESULTS

Existing paediatric dose recommendations

- Current dose recommendations for benznidazole in WHO guidelines, national control programs, and clinical textbooks show some variations in the recommended specified dose range in mg per kg of bodyweight (Table 1). In general, the recommended treatment dose for children is higher than for adults.
- None of the recommendations offer accurate dose guidance for young children with the available 100mg tablet.

Table 1. Benznidazole dose recommendations for *T. cruzi* infections

Source	Dose recommendation
WHO – Chagas control TEG[2]	Congenital infections: 5–10mg/kg/day
WHO – Model prescribing information[3]	Children ≥12 yrs: 5–7mg/kg/day Children <12yrs: 10mg/kg/day
Hoffman-La Roche package insert	Children ≥12 yrs: 5–7mg/kg/day Children <12yrs: 10mg/kg/day
Roche. Radanil® insert package Roche. Rochagan® insert package	5–8 mg/kg/day bid PO for 60 days Adults: 5–7mg/kg/day bid PO for 30–60 days Children <12yrs: up to 10mg/kg/day for the initial 10–20 days
Manson's Tropical diseases	Adults: 7.5mg/kg/day bid for 60 days Children: 10mg/kg/day bid for 60 days
Brazilian Ministry of Health[4]	Adults: 5mg/kg/day bid PO for 60 days Children: 5–10mg/kg/day bid or tid PO for 60 days
Brazilian Ministry of Health[5]	Acute phase, congenital infection, immunocompromised patients, and transplants: 8mg/kg/day bid PO for 60 days
Guías para la atención al paciente infectado con *trypanosoma cruzi* (enfermedad de chagas), Ministerio de salud[6]	All age groups: 5-7 mg/kg/day bid or tid PO for 60 days

WHO: World Health Organization; TEG: Technical Expert Group; bid: split over two doses per day; tid: split over 3 doses per day; PO: oral treatment.

Current treatment data and practice

- Clinicians and scientists provided anthropometric and dosing information from 2779 treatments from 10 different sources, with over 99% of data for children <18 years.
- The age distribution across the patient population is described in Figures 2a and 2b.

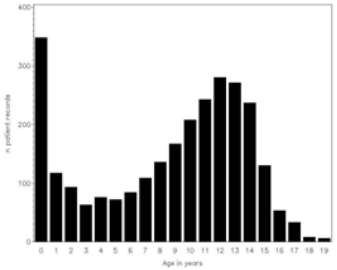

Figure 2a. Age distribution of patient (n = 2779).

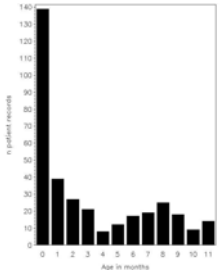

Figure 2b. Age distribution in infants (n = 247).

Weight-for-age distribution and prescribed intake dose

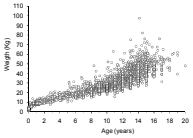

Figure 3a. Weight by age across age groups (n=2378)

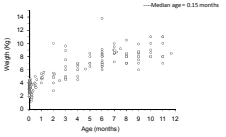

Figure 3b. Weight by age in infants (n=237)

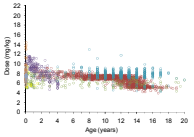

Figure 3c. Benznidazole intake dose across age groups (n=2424)

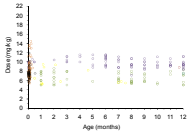

Figure 3d. Benznidazole intake dose in infants (n=317)

Note: Different colours refer to different treatment centres.

- Paediatric tablet strength options are presented in figure 4. Grey rectangles indicate applied specified dose ranges: 5–10mg/kg BID for children <12 years and 5–7mg/kg/day BID for children ≥12 years and adults.

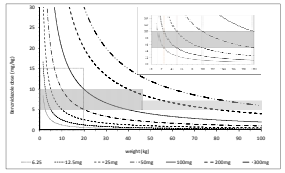

Figure 4. Tablet strength options

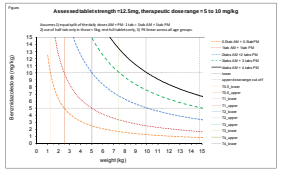

Figure 5. Suggested tablet strength

- To define tablet strength, the following conditions were taken into consideration:

  The acceptable dose range of 5–10mg/kg and an ideal regimen of a single tablet/intake (max of 2 tablets/day), with a single split.

- With the regimen characteristics and a consensus on the therapeutic dose range of 5–10mg/kg/day , the selected tablet strength was 12.5mg **(Figure 5)**.

CONCLUSION

- The proposed new paediatric formulation of 12.5mg benznidazole will markedly improve dosing accuracy in children <10kg, and focus on infants with congenital *T. cruzi* infections. Each year, an estimated 15.000 congenital infections occur in Latin America. Treatment of congenital cases is recommended independent of the presence of symptoms, as cure rates are highest and almost 100% if treatment occurs in the first year of life. Treatment has been proven safe for most treated children.
- Additionally, the combination of a 12.5mg paediatric tablet and the existing 100mg tablet would provide a (bid) dose regimen option with which adult and children patients could receive the therapeutic dose. Only two groups would require ½ tablet fractions: low-birth-weight babies (<2500g) (½ paediatric tablet) and children weighing between 10 and 20 kg (½ adult tablet).
- The main limitation to this approach is the lack of paediatric pharmacokinetic (PK) data. This work and the global WHO dose recommendation we applied are based on clinical experience of efficacy and safety in children rather than PK data. Also, the use of historical patient data has limitations, as the patient sample may be prone to bias and not be representative of the general Chagas patient population. However, our approach determined a tablet strength for use within the current global treatment guidelines, and dosing experience in patients treated with benznidazole.
- The review of current treatment recommendations and practices, and empirical clinical experience helped to determine an appropriate, paediatric tablet strength of benznidazole for Chagas control programs that will improve dosing accuracy of treatments in infants with congenital *T. cruzi* infections, an increasingly important patient group. Paediatric formulations are urgently needed for several drugs on the essential medicines list.

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