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 Chagas disease. 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.

METHODOLOGY

- The following steps were used to determine the appropriate paediatric tablet strength and formulation:
  - Verification of target paediatric therapeutic dose range for benznidazole: review of available paediatric dose recommendations for benznidazole in WHO guidelines, national control programs, and textbooks.
  - Review of paediatric dosage 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 disease control programs discussed the required regimen characteristics such as drug formulations (ie. liquid solutions, dispersible tablets), method and acceptability of the use of tablet forms, and other characteristics to determine the paediatric tablet strength.
- Ethics clearance: Not applicable. Secondary analyses were done on anonymised data.

RESULTS

- Current dose recommendations for benznidazole in WHO guidelines, national control programs, and clinical practice 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 for acute phase congenital infection, immunocompromised patients, and transplants: 5-7 mg/kg/day bid PO for 60 days.
- Some of the recommendations offer accuse dose guidelines for young children with the available 100mg tablet.

CONCLUSION

- The proposed new paediatric formulation of 12.5mg benznidazole will markedly improve dose accuracy in children <10kg, and focus on infants with congenital 7 crux 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 (d) 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 pharmaco-economic (P/C) data. This work only uses the global WHO dose recommendation and a breakpoint for the lower and upper dose range cut-off dose. Only two groups would require ½ tablet fractions: lower and upper dose range cut-off dose. Only two groups would require ½ tablet fractions: lower and upper dose range cut-off dose.
- 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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1) Children below 20 kg are treated with fractions of these tablets.

Table 1. Benznidazole dose recommendations for T. cruzi infections

<table>
<thead>
<tr>
<th>Dose recommendation</th>
<th>Weight (Kg)</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO – Chagas control TEG</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
</tr>
<tr>
<td>WHO – Model prescribing</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
</tr>
<tr>
<td>Hoffmann-La Roche package insert</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
</tr>
<tr>
<td>Roche/Roche packaged insert</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
</tr>
<tr>
<td>Mencos/Tropical-diseases</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
</tr>
<tr>
<td>Brazilian Ministry of Health</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
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<td>WHO – World Health Organization: TEG</td>
<td>10-14 yrs</td>
<td>6-8 mg/kg/day</td>
</tr>
</tbody>
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**Table 2.** Paediatric tablet strength options for T. cruzi infections.