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.

Table 1. Benznidazole dose recommendations for T. cruzi infections

<table>
<thead>
<tr>
<th>WHO – Chagas control TEG</th>
<th>Congenital infection: 5–10mg/kg/day</th>
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</thead>
<tbody>
<tr>
<td>WHO – Model prescribing</td>
<td>Children &lt;12 yrs: 5–7mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Children ≥12 yrs: 10mg/kg/day</td>
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<tr>
<td>Hoffmann-La Roche package inert</td>
<td>Children &lt;12 yrs: 3–5mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Children ≥12 yrs: 10mg/kg/day</td>
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<tr>
<td>Roche Redfern – inert package</td>
<td>Roche, Hoffmann-La Roche 300mg tablet</td>
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<tr>
<td></td>
<td>Adults: 5mg/kg/day bid PO for 30–60 days</td>
</tr>
<tr>
<td></td>
<td>Children &lt;12 yrs: up to 10mg/kg/day bil PO for 10–20 days</td>
</tr>
<tr>
<td>Chagas Ministry of Health</td>
<td>Adults: 7.5mg/kg/day bid PO for 60 days</td>
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<tr>
<td></td>
<td>Children 5–10mg/kg/day bid or tid PO for 60 days</td>
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<tr>
<td>Benznidazole 50mg/50mg</td>
<td>Adults: 12.5mg bid PO for 60 days</td>
</tr>
<tr>
<td></td>
<td>Children: 5–10mg/kg/day bid or tid PO for 60 days</td>
</tr>
</tbody>
</table>

Guanos para el examen al paciente infectado con trypanosoma cruzi (paediatrico), (MINISTERIO DE SALUD Y DEPORTES, Ministerio de Salud de la Nación, Argentina). WHO: World Health Organization; TEG: Technical Expert Group; bid: split over two doses per day; tid: split over three doses per day.

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 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 (e.g. liquid solutions, dispersible tablets), need and acceptability of the use of tablet formulations, and other factors to determine the paediatric tablet strength.
- Ethics clearance: Not applicable. Secondary analyses were done on anonymized data.

RESULTS

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 that for adults.

- None of the recommendations offer accurate dose guidance for young children with the available 100mg tablet.

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

CONCLUSION

- The proposed new paediatric formulation of 12.5mg benznidazole will markedly improve dosing accuracy in children <10kg, and focus on children with congenital 7.5mg/kg 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 all treated children.

- Additionally, the combination of a 12.5mg paediatric tablet and the existing 100mg tablet would provide a (dual) dose regimen option with which adult and children patients could receive the therapeutic dose. Only two groups would require ¼ tablet fractions: (low-weight babies (≤25kg), 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 will enhance the global WHO dose recommendation for benznidazole and drug education in drug delivery. Based on the substantiated 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 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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