EFFICACY, SAFETY AND POPULATION PHARMACOKINETICS OF BENZNIDAZOLE IN CHILDREN

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CHAGAS DISEASE

• The infection occurs mostly in children by vectorial or congenital route

• Treatment of children with benznidazole is effective and well tolerated

• If untreated, CD leads to cardiac morbidity years or decades after infection

• CD is endemic in Latin America but, due to migration, infected patients have been found in USA, Europe, Australia, Japan
Benznidazole

- Only 2 PK studies of benznidazole have been carried out, and only with adults, in the 70’s
- Pediatric dose adapted from adult dose (in mg/kg),
- Off-label use of drugs is common in children
- **No information** about pediatric PK is available
“There is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents.”

AAP Committee on Drugs. *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations* - Pediatrics 1995;95:286
Children unlike adults have good tolerance to benznidazole but WHY? Children are not little adults...

Children and adults differ in:
- Absorption
- Distribution
- Renal function (excretion)
- Hepatic function (metabolism)
- Pharmacodynamics:
  - therapeutic response
  - adverse reactions
  - mechanisms of disease

Kearns et al. NEJM 2003. 349:1157-1167
Ontogeny Cytochrome P450 Enzymes
Changes over time

Ontogeny of CYP Enzymes

- CYP3A4
- CYP1A2
- CYP2D6
- UGT2B7

Percent Adult Activity

Kearns GL et al. NEJM 349: 1157, 2003
Background

Chagas disease infects children and kills them when they are adults

Information about pharmacokinetics of benznidazole in children and specially in infants is vital to ensure a good therapeutic response
Population PK BNZ in children

1\textsuperscript{st} study in children

Clinicaltrials.gov registry # NCT00699387

- Prospective study in children 2 – 12 years old with Chagas disease
- Patients were enrolled at Buenos Aires Children’s Hospital, Argentina
  - Benznidazole (Radanil®, Roche) 100 mg tablets
  - Dose: 5-8 mg/kg/d bid for 60 days
  - Compliance evaluated by pill counts
PopPK BNZ in children

- Samples for PK were obtained at randomly pre-assigned times (3 per patient)
- Benznidazole in plasma was measured by HPLC-UV
- PopPK modeling was performed with NONMEM software (non linear mixed effects analysis)
Patients eligible for the study: 44

Refused to participate: 2
Lived out of the city (>100 Km): 2

Enrolled: 40
Age: 7.3 years (range 2.1 – 12)

Completed treatment: 37
BZ: 6.4 mg/kg/day (range 5 – 8.7)
118 samples for PopPk analysis

Withdrawn due to moderate ADR: 2
Loss to follow up: 1

All children treated had a positive treatment response, with negativization of PCR for T. cruzi DNA, and marked decrease in anti T. cruzi antibody titers
PopPK BNZ in children

• Adverse drug reactions (ADR) were observed in 3 patients:
  – Mild rash (20 days of treatment)
  – Moderate prurigo (8 days of treatment)
  – Generalized rash (10 days of treatment)

• All ADRs resolved with symptomatic treatment (antihistamines) and temporary drug discontinuation

• In 2 cases rash reappeared with drug reintroduction, and required patient withdrawal
PopPK BNZ in children

Population PK parameters:

• Median Cmax 4.3 mg/L (range 1 – 12.2)
• PopPK parameters:
  – CL : 1.43 L/hr
  – Vd : 30.3 L
  – Ka : 0.185 h⁻¹
Comparative results (children and adults)

<table>
<thead>
<tr>
<th>Css (7mg/kg/day)</th>
<th>Children</th>
<th>Adults</th>
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</thead>
<tbody>
<tr>
<td>Median (mg/L)</td>
<td>4.53</td>
<td>10.96</td>
</tr>
<tr>
<td>95% CI (median)</td>
<td>[3.7 – 5.6]</td>
<td>[7.7 – 15.4]</td>
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<table>
<thead>
<tr>
<th>Css (7mg/kg/day)</th>
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<tr>
<td>Median (mg/L)</td>
<td>3.18</td>
<td>6.99</td>
<td>10.96</td>
</tr>
<tr>
<td>95% CI (median)</td>
<td>[2.5 – 3.9]</td>
<td>[5.1 – 8.9]</td>
<td>[7.7 – 15.4]</td>
</tr>
</tbody>
</table>

Weight-corrected clearance (popPK)

Children have higher clearance

(Raaflaub et al. 1980)
Steady state concentrations (popPK)

Children have lower concentration than adults. (Raafflau et al. 1980)
PK Benznidazol

Adverse events in a cohort of 107 children treated with benznidazole


Children have lower concentration

Children have lower incidence of ADRs

Simulated Css (2-12 yo)
95% prediction interval (1000 simulations)
Conclusions

If these results are confirmed, dose reduction in children older than 7 years and in adults should be considered.
POPULATION PHARMACOKINETICS STUDY OF BENZNIDAZOLE IN CHILDREN WITH CHAGAS DISEASE-
THE 1ST STUDY IN CHILDREN YOUNGER THAN 2 YEARS

Clinicaltrials.gov registry # NCT01549236
DNDi-CD-PEDBZ-001

DNDi
Drugs for Neglected Diseases initiative
Population Pharmacokinetics Study of Benznidazole in Children with Chagas Disease
Population PK BNZ in children
1st study in infants

• Prospective study in children 1d – 12 years old
• Multicentric study: PEDCHAGAS group
• Treatment: 12.5mg or 100mg Bz Tablet, (LAFEPE), 7.5 mg/Kg/day PO in two daily doses, for 60 days.
• Samples for PK were obtained at randomly pre-assigned times (5 per patient) 100µL of blood collected in filter-paper
• Benznidazole in plasma was measured by HPLC-MS-MS
• PopPK modeling was performed with NONMEM software (non linear mixed effects analysis)
Patients eligible for the study: 83

Enrolled: 81
Age: >2a: 40; < 2a: 41 (8 newborn)

Screening failure: 2

30 ADRs: 14 rash, 11 GI, 4 lab, 1 SAE

Withdrawn due to ADR: 3
Loss to follow up: 2

Completed treatment: 76
BZ: 7.5 mg/kg/day
45 received 12.5mg tablet
386 samples for PopPk analysis

All children had a positive treatment response, with negativization of PCR for *T. cruzi*. 
Pk sampling: micro-samples of 100µL collected in filter-paper
Lactating and pregnant women are a neglected population

In population in endemic areas with high pregnancy rates opportunities for treatment of CD are scarce.

Treatment during lactation may provide a good opportunity due to short interpregnancy period

We need information about safety of breastmilk during maternal CD treatment
TRANSFER OF BENZNIDAZOLE TO BRESTMILK

Clinicaltrials.gov # NCT01547533

Proof of concept, prospective cohort study of lactating women with CD treated with Benznidazole
Results

12 lactating mothers with CD were treated with BZ p.o. 5.66 mg/kg/día (3.6-6.7) máx. 400 mg

Assuming a daily milk intake of 150ml/kg the estimated BZ dose is 0.6 mg/kg/day

BZ in plasma: 4.5 mg/l (SD 4.11, range 1.3-12.57)
BZ in breast milk: 3.8 mg/l (SD 1.06, range 2.4-5.9)

Ratio: Milk/plasma

RID = maternal dose /kg infant dose/ kg

10.9, SD 3.2 (range 5.4-16.8)

X 0.99 (SD 0.7)

Infant dose: 10% of maternal dose (mg/kg)

RID: Relative infant dose
Lactation is not a contraindication for CD treatment

The baby is not at risk during maternal treatment
Hospital de Niños, Buenos Aires
Altcheh Jaime
Moroni Samanta
García Bournissen Facundo
Moscatelli Guillermo
Ballering Griselda
Freilij Hector
Bisio Margarita
Fctad química, Univ de La Plata
Marson Elena
Mastrantonio Guido
DNDi
Isabela Ribeiro
Jayme Fernandez

Hospital de Niños, Jujuy
Caruso Martin
Maria Rosa Miranda
Ma Graciela Valdez
Hospital Materno infantil, Salta
Monla Celia
Centro de Chagas, Sgo del Estero
Moran Lucrecia
Ledesma Eduardo
Rodriguez Teresa
Inst. Nac. Parasitología
Riarte Adelina
Ingebi
Alejandro Schijman
Pharmacokinetics Studies of Benznidazole

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PEDCHAGAS
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Gracias!
Thank you!