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XXVIII Brazilian Annual Meeting of Applied Research on Chagas Disease,
XVI Brazilian Annual Meeting of Applied Research on Leishmaniasis and
III Latin American Congress on Travel Medicine

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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.”

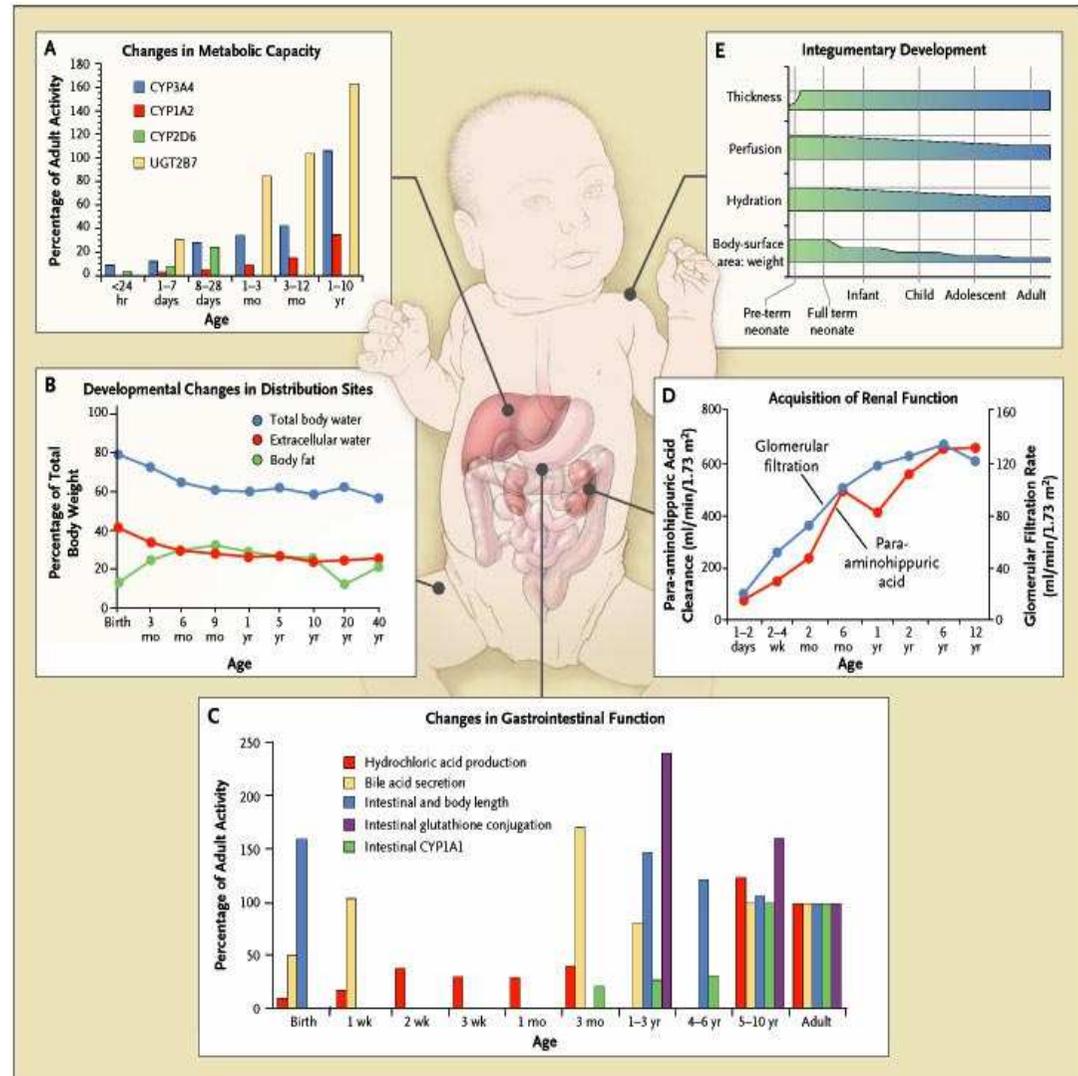
AAP Committee on Drugs. *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations* - Pediatrics 1995;95:286



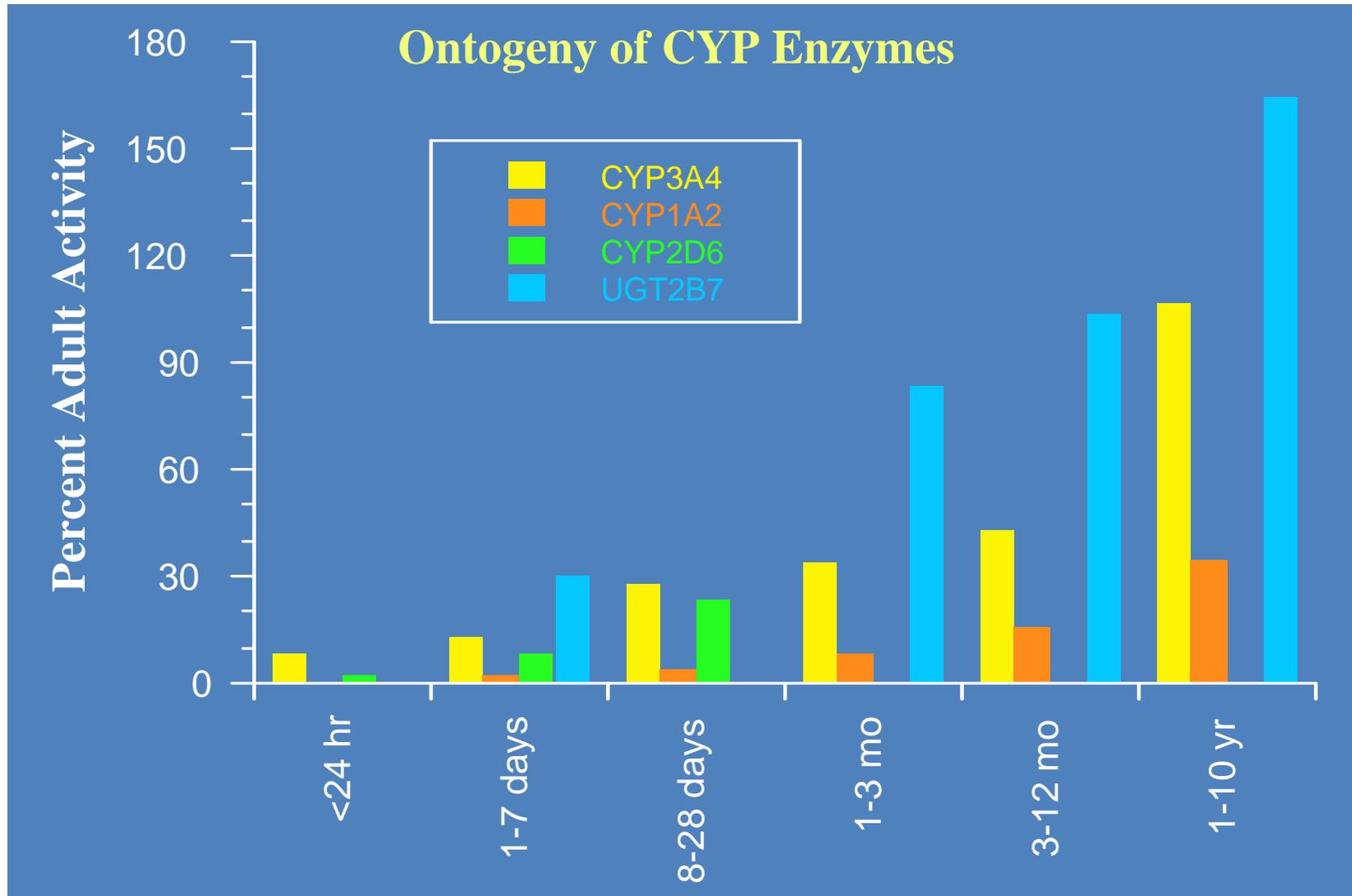
Children unlike adults have good tolerance to benznidazole but WHY? Children are not little adults...

Children and adults differ in:

- × Absorption
- × Distribution
- × Renal function (excretion)
- × Hepatic function (metabolism)
- × Pharmacodynamics:
 - × therapeutic response
 - × adverse reactions
 - × mechanisms of disease



Ontogeny Cytochrome P450 Enzymes Changes over time



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

1st study in children

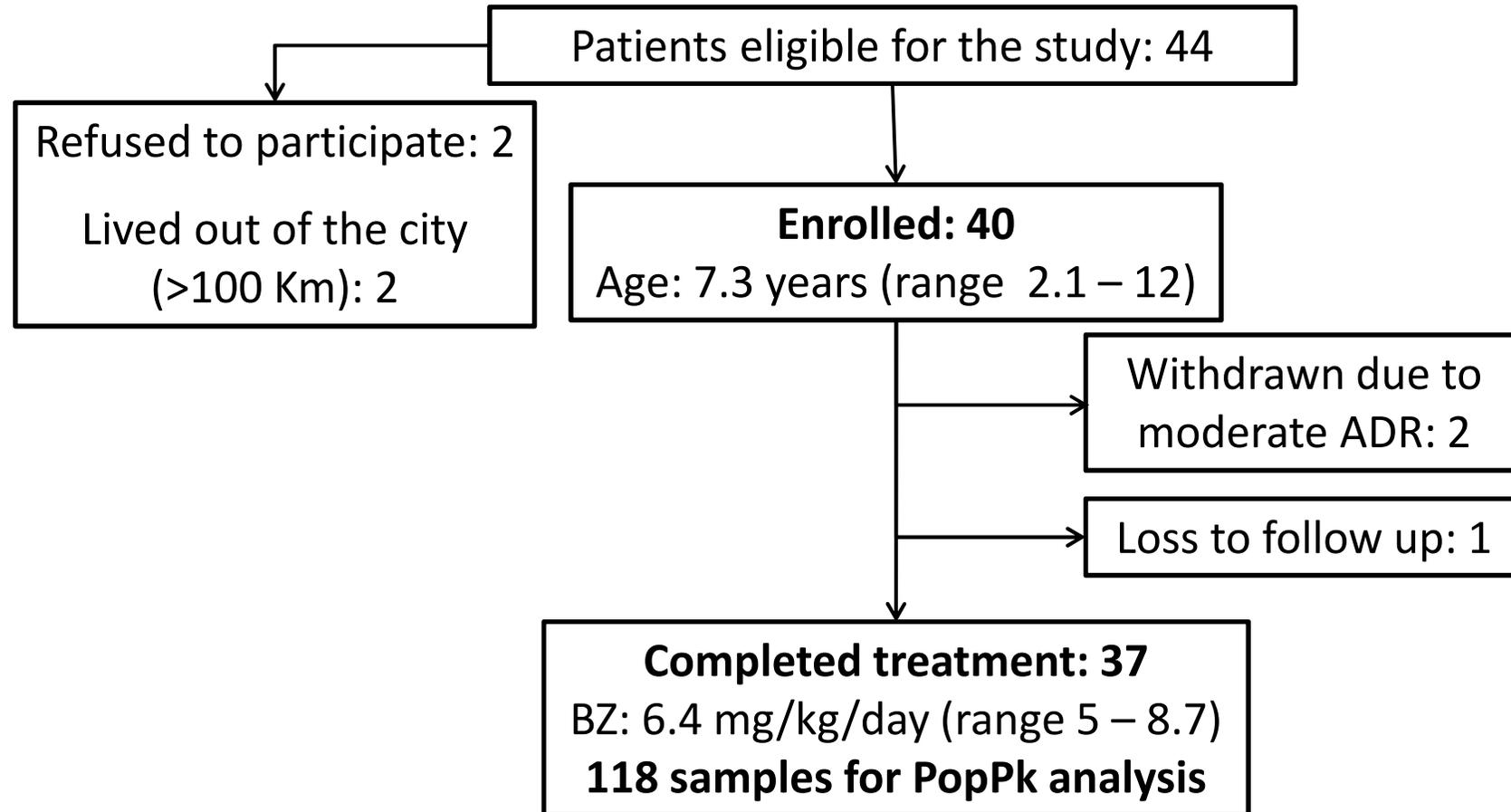
Clinicaltrials.gov registry # NCT00699387

- 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)

Study Flow Chart



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 C_{max} 4.3 mg/L (range 1 – 12.2)
- PopPK parameters:
 - CL : 1.43 L/hr
 - V_d : 30.3 L
 - K_a : 0.185 h⁻¹

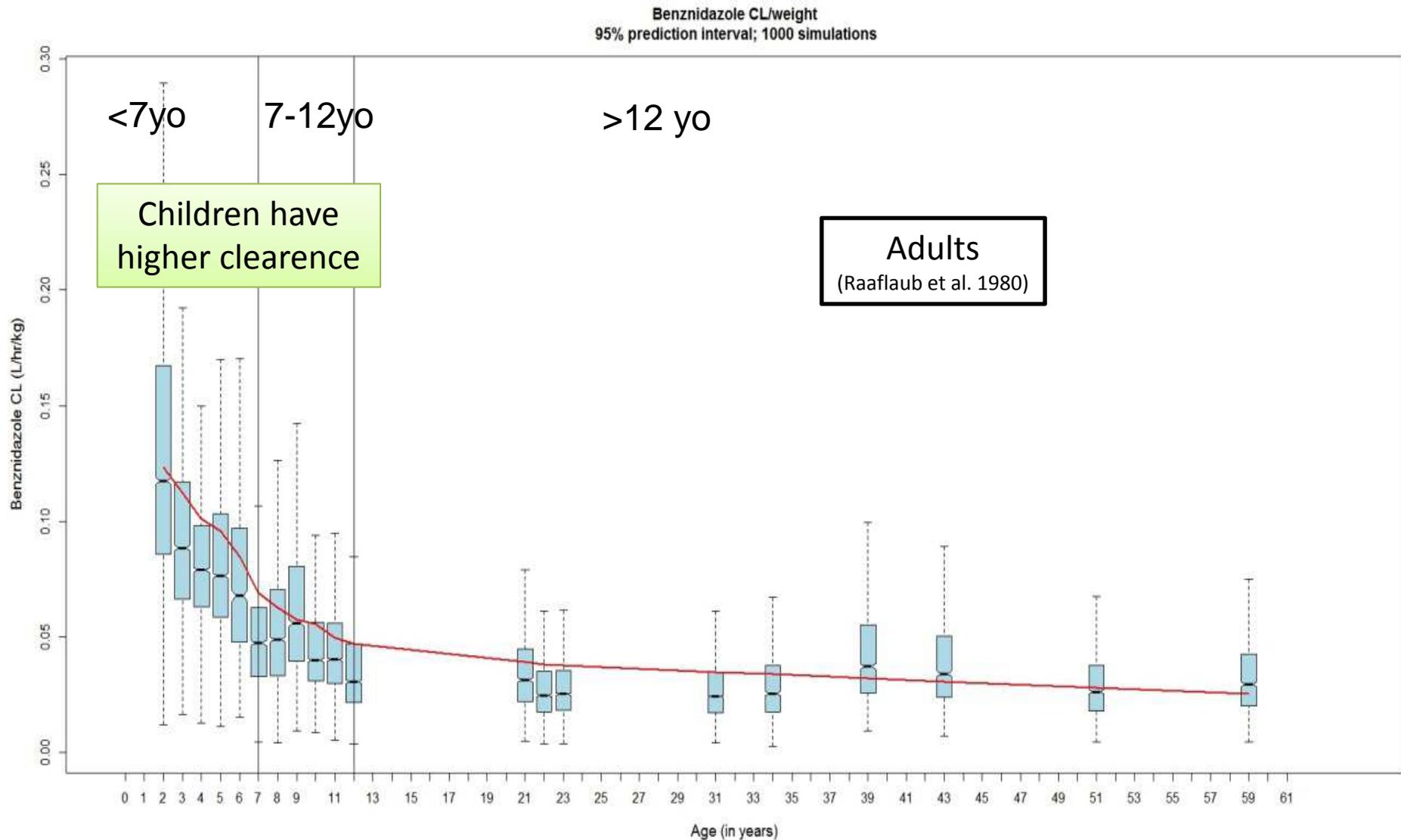
Comparative results (children and adults)

Css (7mg/kg/day)	Children	Adults
Median (mg/L)	4.53 \neq	10.96
95% CI (median)	[3.7 – 5.6]	[7.7 – 15.4]

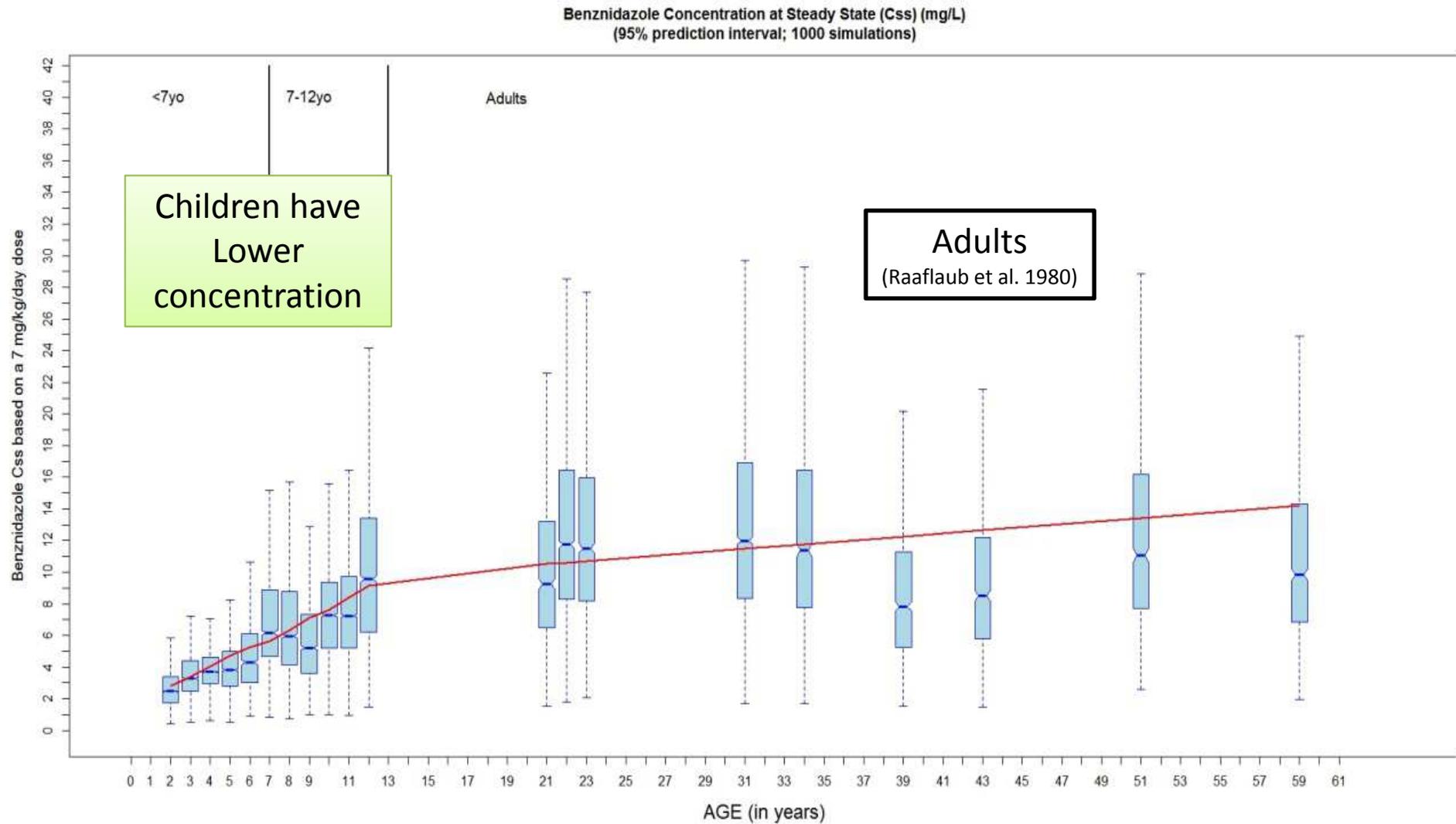
Css (7mg/kg/day)	2-7yo	7-12yo	Adults
Median (mg/L)	3.18 \neq	6.99 \neq	10.96
95% CI (median)	[2.5 – 3.9]	[5.1 – 8.9]	[7.7 – 15.4]

Adult data (re-analyzed) from: Raaflaub J. Arzneimittelforschung. 1980;30(12):2192-4.
Multiple-dose kinetics of the trypanosomicide benznidazole in man.

Weight-corrected clearance (popPK)



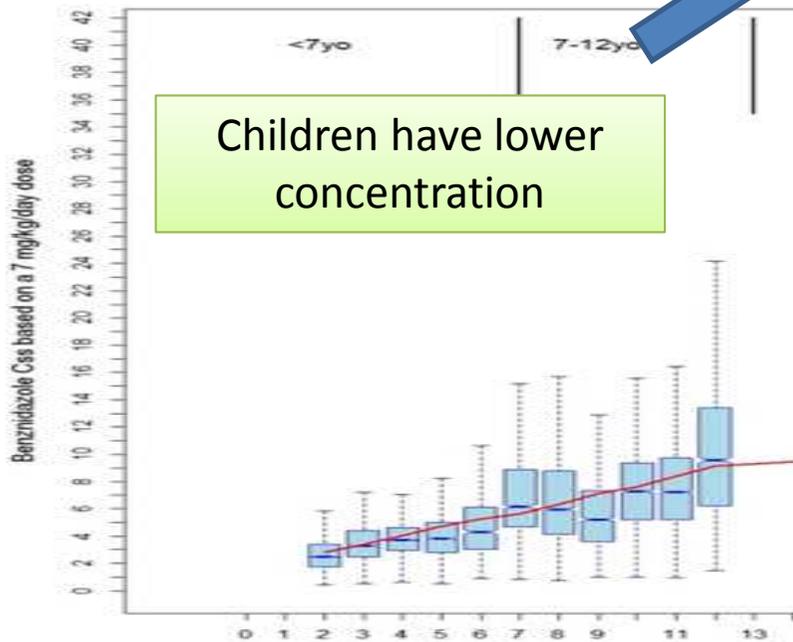
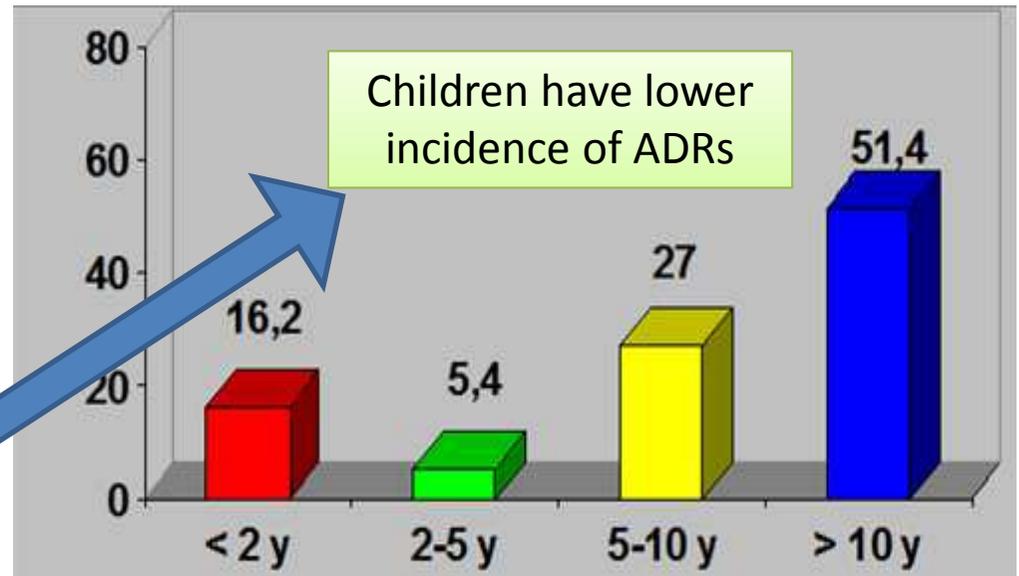
Steady state concentrations (popPK)



PK Benznidazol

Adverse events in a cohort of 107 children treated with benznidazole

Altchek J, Moscatelli G, Moroni S, Garcia-Bournissen F, Freilij H. *Pediatrics*. 2011 Jan;127(1):e212-8.



Simulated C_{ss} (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



DNDi

Drugs for Neglected Diseases *initiative*



INP



Sgo del Estero



Jujuy



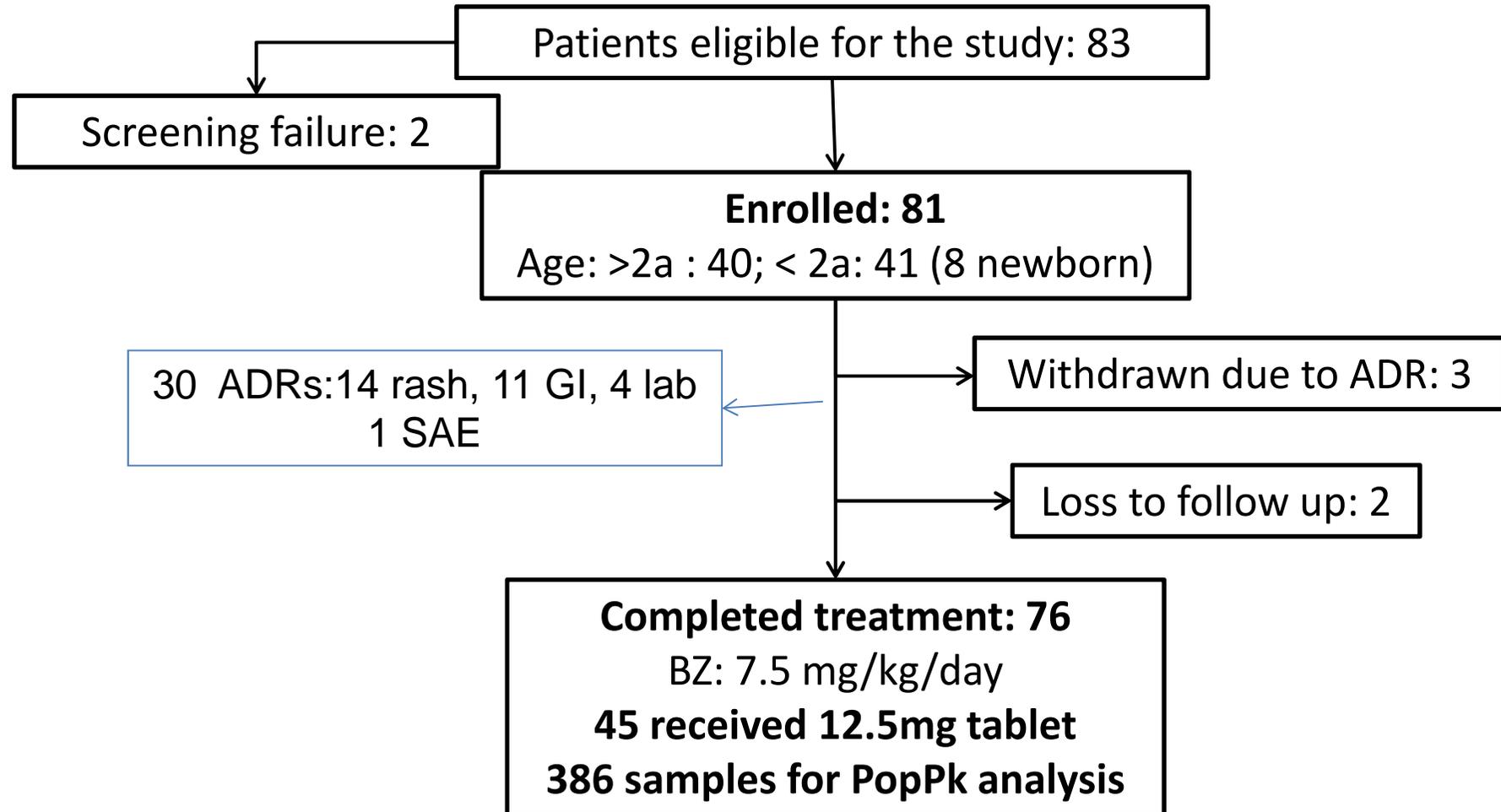
Salta

Population PK BNZ in children

1st study in infants

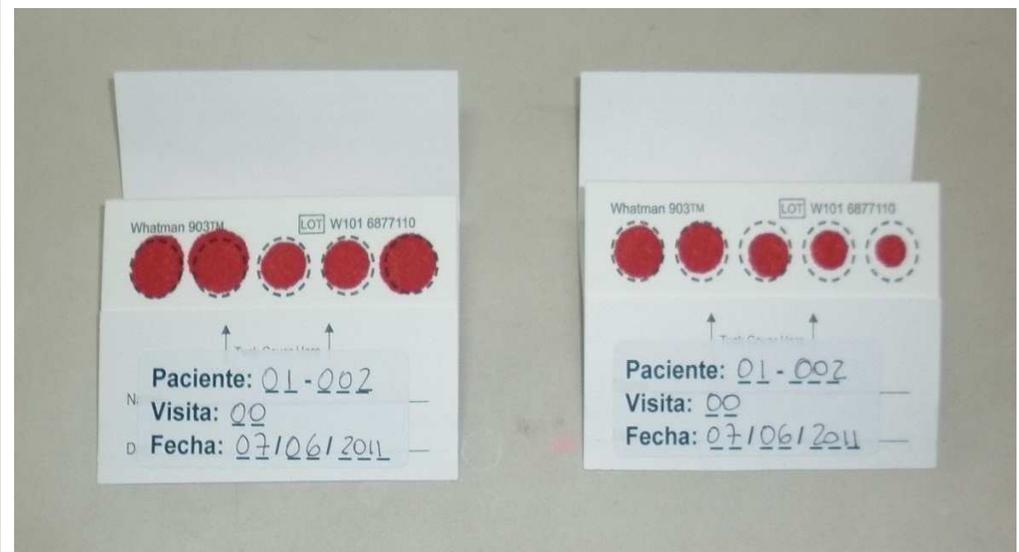
- Prospective study in children 1d – 12 years old
- Multicentric study: PEDCHAGAS group
- Treatment: 12.5mg or 100mg Bz Tablet, (LAFEPE), 7.5 mg/Kg/day PO in two daily doses, for 60 days.
- Samples for PK were obtained at randomly pre-assigned times (5 per patient) 100µL of blood collected in filter-paper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

Preliminary results



All children had a positive treatment response, with negativization of PCR for *T. cruzi*

Pk sampling: micro-samples of 100 μ L collected in filter-paper



Other study....

- **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 BREASTMILK

Clinicaltrials.gov # NCT01547533

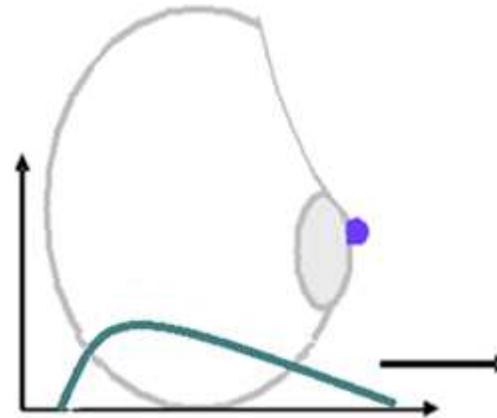
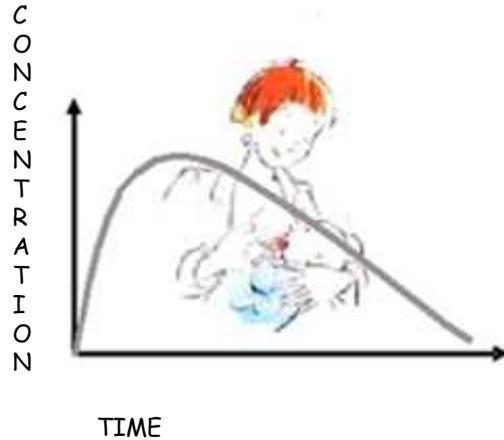
**Proof of concept, prospective cohort
study of lactating women with CD
treated with Benznidazole**



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)

$$RID = \frac{\text{maternal dose / kg}}{\text{infant dose / kg}}$$

Ratio: Milk/plasma

X 0.99 (SD 0.7)

10.9 , SD 3.2 (rango 5.4-16.8)

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

RID: Relative infant dose

TRANSFER OF BENZNIDAZOLE TO BREASTMILK

- Lactation is not a contraindication for CD treatment
- The baby is not at risk during maternal treatment



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CHAGAS
GNOSTICO! DIAGNOSTICO! DIAGNOSTICO!
TRATAMIENTO! TRATAMIENTO!



Pharmacokinetics Studies of Benznidazole

Red Pediátrica para Estudios Clínicos de la
Enfermedad de Chagas

PEDCHAGAS



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Gracias!
Thank you!