

Limited infant exposure to benznidazole through breast milk during maternal treatment for Chagas disease

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ABSTRACT

Background Benznidazole (BNZ) is safe and effective for the treatment of paediatric Chagas disease. Treatment of adults is also effective in many cases, but discouraged in breastfeeding women because no information on BNZ transfer into breast milk is available. We aimed to evaluate the degree of BNZ transfer into breast milk in lactating women with Chagas disease. **Patients and methods** Prospective cohort study of lactating women with Chagas disease treated with BNZ administered for 30 days. Patients and their breastfed infants were evaluated at admission, the 7th and 30th day of treatment (and monthly thereafter, for 6 months). BNZ was measured in plasma and milk by high performance liquid chromatography. The protocol was registered in ClinicalTrials.gov (#NCT01547533).

Results 12 lactating women with chronic Chagas disease were enrolled (median age 28.5 years, range 20–34). Median BNZ dose was 5.65 mg/kg/day twice daily. Five mothers had adverse drug events (45%), but no adverse drug reactions or any untoward outcomes were observed in the breastfed infants. Median milk BNZ concentration was 3.8 mg/L (range 0.3–5.9) and 6.26 mg/L (range 0.3–12.6) in plasma. Median BNZ milk to plasma ratio was 0.52 (range 0.3–2.79). Median relative BNZ dose received by the infant (assuming a daily breast milk intake of 150 mL/kg/day) was 12.3% of the maternal dose per kg (range 5.5%–17%).

Conclusions The limited transference of BNZ into breast milk and the reassuring normal clinical evaluation of the breastfed babies suggest that maternal BNZ treatment for Chagas disease during breast feeding is unlikely to present a risk for the breastfed infant.

Trial registration number ClinicalTrials.gov NCT01547533.

INTRODUCTION

Chagas disease, or *American trypanosomiasis*, is a parasitic zoonosis endemic to the Americas caused by infection with *Trypanosome cruzi*.^{1–3} The disease presents with a short acute phase followed by a chronic phase that, years later, leads to the development of cardiac and/or digestive complications in up to 30% of infected patients.^{4 5} There are approximately 10 million people infected in Latin America, predominantly poor and medically underserved. Recently, Chagas disease has become a global health problem expanding to virtually all regions of the world via immigration, with many cases reported in Europe and North America.^{2 6}

What is already known on this topic

- ▶ Treatment of Chagas disease with benznidazole is discouraged during lactation due to absence of information on its transfer into breast milk.
- ▶ Benznidazole is considered safe and effective during childhood for paediatric Chagas disease.

What this study adds

- ▶ This is the first study to obtain benznidazole concentrations during breast feeding, showing that transference of benznidazole into breast milk is limited.
- ▶ Maternal treatment for Chagas disease with benznidazole during breast feeding is unlikely to be a risk for the breastfed infant.

Only two drugs, nifurtimox and benznidazole (BNZ), are currently available for the treatment of Chagas disease, both with similar effectiveness and limitations.^{3 7} Given the empirical nature of their discovery and development, these drugs have been used without a clear understanding of their mechanisms of action, pharmacokinetics or toxicokinetics. Both drugs are associated with a high risk of toxicity in adults, especially dermatological reactions,^{3 7} but the incidence of adverse drug reactions (ADRs) is much lower in infants and children.^{8–12} BZN is the most commonly used drug in South America for the treatment for Chagas disease, due to availability issues.³

Due to limited safety data, women rarely receive treatment for Chagas disease during lactation due to the perceived risk of exposing infants to these drugs through breast milk. On the other hand, discontinuation of breast feeding to allow maternal treatment is not advisable given that breast milk is the ideal primary nourishment for newborns as well as a source of growth, immunological and cognitive development factors for infants.^{13 14} However, in areas with high birth rates and limited access to healthcare, the postpartum breastfeeding period may be the only time when a woman may be amenable to treatment for Chagas disease. The currently perceived contraindication to treating

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with BNZ during lactation, so far unsubstantiated by any evidence, may lead to lost opportunities for treating these women.¹⁵

The aim of this study was to evaluate, for the first time, the transfer of BNZ into breast milk in lactating women with Chagas disease in order to clarify the risks of exposure to their babies and provide support for evidence-based recommendations for the management of Chagas disease during lactation.

POPULATION AND METHODS

Twelve lactating women with chronic Chagas disease and their respective breastfed infants were enrolled in the Parasitology and Chagas Service at Buenos Aires Children's Hospital 'Ricardo Gutierrez' between July 2011 and February 2012. Women had a diagnosis of Chagas disease by at least two serological reactive tests for antibodies against *T. cruzi* (ELISA, Wiener Laboratory, Rosario, Argentina; Indirect Hemagglutination, Polychaco Laboratory, Buenos Aires, Argentina).

Exclusion criteria included known medical conditions that might affect interpretation of the results (e.g. significant systemic diseases), positive pregnancy test, and a history of hypersensitivity to BNZ or previous treatment with the drug. None of the included patients were taking any other medications.

Treatment

Lactating women received BNZ orally 5–8 mg/kg/day twice daily (100 mg BNZ tablets, Radanil; Roche, Sao Paulo, Brazil), for 30 days.

A detailed clinical history, physical examination as well as laboratory routine tests were obtained at diagnosis and at 7 and 30 days during treatment.

Treatment response was evaluated by *T. cruzi* specific real-time PCR performed at diagnosis and the end of treatment.^{16 17} Patients were instructed to use contraception during the BNZ treatment and a pregnancy test was performed before enrolment.

Diagnosis of congenital Chagas disease

All infants younger than 8 months old were monitored for Chagas disease using direct parasitological tests (microhaematocrit test). Infants with negative parasitemia, but positive serology, were retested by serology at 8 months of age.¹¹ Serology by two serological tests for antibodies against *T. cruzi* was used for children older than 8 months of age. All children were assessed in their growth and psychomotor development by a paediatrician with experience in treatment of Chagas disease. Paediatric assessments were performed at days 0, 7 and 30 of maternal treatment, and monthly thereafter, for at least 6 months.

Analytical methods

Breast milk samples, approximately 30 mL each, were collected before the first BNZ dose and on the 7th and 30th day after starting BNZ treatment. Some samples were prefeeding and some postfeeding but, unfortunately, this information was not systematically collected for all samples. Milk was mixed, total volume recorded and an aliquot (up to 20 mL) was taken for analysis. The milk samples were stored at -20°C prior to analysis.

Venous blood was sampled in heparinised tubes at the same time points as milk. Samples were centrifuged at 3000 g for 10 min and plasma stored at -20°C and lyophilised prior to analysis.

High performance liquid chromatography was used to determine BNZ concentration in plasma and milk, as previously described.^{18 19} The limit of detection (LOD) and limit of quantitation (LOQ) for plasma were 0.14 and 0.32 mg/L, respectively. The LOD and LOQ for milk were 0.3 and 0.9 mg/L, respectively.

Milk to plasma ratios were calculated from single milk and plasma concentration measurements. An infant milk intake of 0.15 L/kg/day was assumed;^{20–22} this value was multiplied by single-point milk concentration to give the absolute infant dose of BNZ in $\mu\text{g}/\text{kg}/\text{day}$. The infant dose was then expressed as a relative infant dose (RID), a percentage of the weight-normalised maternal dose ($\mu\text{g}/\text{kg}/\text{day}$). In cases where more than one RID estimate was available for the same patient, the highest RID was chosen for the statistical calculations.

Ethics

The study protocol was approved by the research and teaching committee and bioethics committees of the Buenos Aires Children's Hospital 'Ricardo Gutierrez'. Written informed consent was obtained from all patients. The protocol was registered in ClinicalTrials.gov (#NCT01547533).

RESULTS

A total of 12 women and their 12 respective babies were enrolled in the study. Median age and weight of the mothers were 27 years (range 20–34 years) and 56 kg (range 45–110 kg), respectively. Median infant age was 5.2 months (range 20 days–13 months) and median weight 7.35 kg (range 4.4–10.2 kg). All infants were healthy, within 25th to 95th percentiles for weight and height for their respective ages. Five children were exclusively breast fed and six also received solid food. Maternal median daily dose of BNZ was 5.65 mg/kg/day (range 3.6–6.6 mg/kg/day) (table 1).

Five mothers (45%) had ADRs: 2 (18%) were mild (transient face and chest rash) and could continue treatment, and 2 (18%) were moderate (generalised rash with itching) and had to discontinue medication after 19 and 22 days of treatment; 1 (9%) patient had a severe ADR (drug reaction with systemic symptoms (DRESS)) after 26 days of treatment and treatment had to be suspended. This was the only case in which breast feeding had to be discontinued due to the severity of the maternal reaction. After hospitalisation, the patient fully recovered; her child had no signs of ADRs at any time.

A total of 10 patients (83%) provided 16 milk samples for the study (one patient withdrew from the study before starting treatment, and another patient stopped treatment due to ADRs before contributing milk samples). Two patients contributed milk samples, but withdrew from the study before treatment completion (at 8 and 14 days, respectively) due to ADRs.

Physical examination and laboratory routine tests were normal, except in the case of the patient with severe ADR who showed 33% reactive lymphocytes and increased liver function tests in the context of DRESS. Despite strong and repeated contraceptive advice, two patients who had discontinued treatment due to ADRs became pregnant about 18 and 19 days after discontinuing treatment. Both pregnancies were uneventful and the babies were healthy, with no complications or problems. Interestingly, both babies were born free of *T. cruzi* infection (i.e. no congenital transmission took place).

Breast milk samples were taken at a median 9 days (range 6–34) into the treatment so that all patients can be assumed to have been at steady state at the time. Median plasma BNZ concentration was 6.26 mg/L (range 0.3–12.6 mg/L) and 3.8 mg/L in milk (range 0.3–5.9). Median milk to plasma BNZ

Table 1 Individual benznidazole (BNZ) levels in maternal plasma and breast milk

Patient ID	Maternal BNZ dose (mg/day)	Maternal BNZ weight-adjusted dose (mg/kg/day)	Sampling times (days after start of treatment)	Plasma		Breast milk			Relative infant BNZ dose (% weight-adjusted maternal dose)*	
				Hours after dose	BNZ concentration (mg/L)	Hours after dose	BNZ concentration (mg/L)	Infant daily dose (mg/kg)*		Milk to plasma*
P1	300	6.6	6	ND	ND	7	2.4	0.36	ND	5.5%
P2	300	5.9	9	12	4.43	9.5	4.4	0.66	0.99	11.2%
P3	400	5.7	7	11	10.13	10	3.8	0.57	0.38	10.0%
P4†	400	6.5	ND	ND	ND	ND	ND	ND	ND	ND
P5†	400	6.5	1	7.5	0.93	ND	ND	ND	ND	ND
P6	300	5.6	9	12	3.19	18.5	4.1	0.62	1.29	11.0%
			30	12.5	3.83	1	3.1	0.47	0.81	8.3%
P7	400	3.6	8	2.5	1.30	10.5	3.1	0.47	2.38	12.9%
			34	62.5	0.30	59.5	0.3	0.05	1.00	1.3%
P8	300	5.6	7	13	7.32	1	5	0.75	0.68	13.4%
			32	15	1.36	15	3.8	0.57	2.79	10.2%
P9	300	5.2	7	2.5	12.57	2	5.9	0.89	0.47	17.0%
			32	13.5	6.61	13	2.0	0.29	0.30	5.6%
P10	400	5.9	9	14	9.53	2	5	0.75	0.52	12.7%
			31	15	5.90	15	2.1	0.32	0.37	5.5%
P11	300	5.3	8	10.5	8.79	10.5	2.9	0.44	0.33	8.2%
			30	9.5	9.75	9.5	4.2	0.63	0.43	11.9%
P12	300	5.4	8	11	10.82	11	5.2	0.78	0.48	14.5%
Median*	300	5.7			6.26		3.8	0.65	0.52	12.3%
IQR	(300; 400)	(5.4; 6.1)			(2.73; 9.59)		(2.8; 4.6)	(0.58; 0.75)	(0.47; 1.29)	(11%; 13.3%)

*Whenever two measurements were available for the same patient, the highest value was chosen for the estimation of the median to avoid biasing results by including multiple values from the same patient.

†Patients P4 and P5 withdrew from the study due to adverse drug reactions before providing breast milk samples; P5 provided an initial plasma sample. ND, not done.

concentration ratio was 0.52 (range 0.3–2.79). There was a positive correlation between plasma BNZ and milk BNZ (figure 1).

Assuming a 150 mL/kg daily milk intake, the estimated median BNZ daily dose received by the infants through breast milk would be 0.65 mg/kg/day, representing a median RID of 12.3% of the maternal weight-corrected daily dose (range 5.5%–17.0%).

No ADRs were observed in the breastfed infants nor any changes in their behaviour, weight progress or other effects

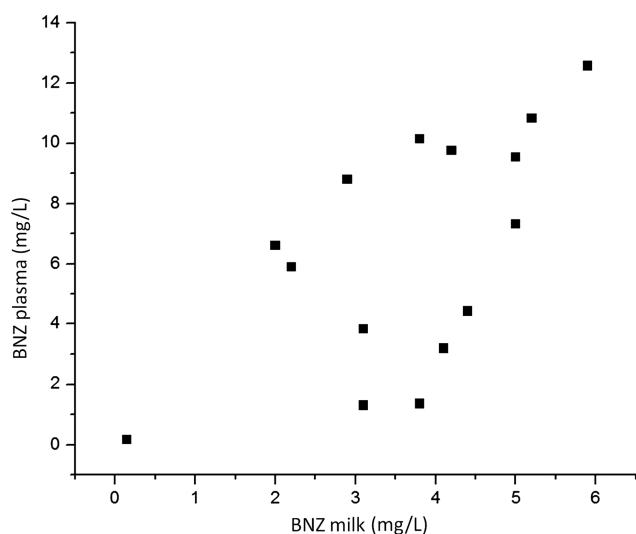


Figure 1 Correlation between plasma benznidazole (BNZ) and milk BNZ concentrations.

potentially attributable to BNZ. All infants were healthy during and after the study, as assessed by paediatricians skilled in the evaluation of paediatric patients with Chagas disease.

At follow-up, nine of the 12 infants (75%) had negative anti-*T. cruzi* antibody titres, ruling out congenital infection. The remaining three infants (25%) were diagnosed with congenital Chagas disease; two infants were diagnosed by serology, and another one by positive parasitaemia by microhaematocrit before maternal treatment was started. All three infants were successfully treated with BNZ with positive serological and PCR response, and no ADRs.

DISCUSSION

Chagas disease can be transmitted to humans by vector transmission, by kissing bugs of the subfamily *Triatominae*, congenitally from mother to infant, and by blood transfusions or organ transplants. Recently, the oral route of infection has been described in small outbreaks linked to food contaminated with parasites.^{3 23–25} Presence of *T. cruzi* in human milk has been rarely demonstrated, almost exclusively in mothers who had bleeding nipples during acute infection. Although the risk for parasite exposure through breast milk has not been clearly established, it is not expected to be significant and maternal Chagas disease is not considered sufficient reason to avoid breast feeding.^{26–28} However, special situations such as breast feeding during the acute phase of the disease, reactivated disease or bleeding nipples should be evaluated with caution.

In rural, underserved, areas of Latin America, contact of young women with the health system outside puerperium may be sporadic. Also, in areas with high numbers of pregnancies per individual, the short inter-pregnancy interval would leave

little time available for treatment of Chagas disease outside of the breastfeeding periods. This situation may force physicians to choose between treating the mother and supporting breast feeding, in spite of current recommendations of exclusive breast feeding for at least the first 6 months of life.¹³ However, the choice between treatment and breast feeding is not without risks, some significant, such as losing the opportunity to treat the mother and hopefully preventing congenital infections in future babies as well as preventing long-term cardiac complications in the mother or, if treatment is chosen over breast feeding, the baby's exposure to water (needed to prepare formula milk) of questionable quality, among many other problems.

We present in this manuscript the outcome of the first prospective study to evaluate the transfer of BNZ into breast milk in women with Chagas disease. Our results show that, assuming a daily milk intake of 150 mL/kg/day, breastfed infants would be exposed to approximately 12% of the maternal weight-corrected BNZ dose. This RID is close to the commonly accepted cut-off of 10% used to guide risk evaluation of drugs during lactation^{29–31} and, given the widely demonstrated safety of BNZ in infants, the resulting BNZ milk concentrations are not expected to lead to exposures that could have any adverse effects on the infant. We do not expect any significant risks of ADRs at exposures that are 5–10 times lower than therapeutic exposures, such as those observed in the infants in this cohort.

Infants and children tolerate therapeutic doses of BNZ better than adults and have a much lower rate of ADRs.^{8–12} No ADRs were observed in the breastfed infants in our study nor any changes in their behaviour, weight progress or any other effects potentially attributable to BNZ, confirming the safety of the drug during breast feeding. The overall observed incidence of ADRs in adults in our cohort (45%) is in agreement with the rate previously described in adults.^{3 7 32}

Transfer of drugs into breast milk is a function of the molecular weight (MW) and maternal plasma level.^{29 30} BNZ is a small molecule (MW=161) with high oral bioavailability and moderate plasma protein binding (50%).³³ On the other hand, our results show clear evidence that the milk concentrations are a function of the plasma concentrations (figure 1). These results follow the general rule stating that the concentrations in human milk of most drugs are usually low and will seldom lead to levels that could produce a pharmacological response in the nursing infant.^{29 34}

A limitation of this study is the small number of infants enrolled, which makes it impossible to rule out uncommon adverse events in the infants. However, relatively large numbers of paediatric Chagas disease patients, including infants and neonates, have been treated with BNZ at therapeutic doses (approximately 8–10 times higher than the expected exposure through breast milk based on our data) for the past few decades in many centres in Latin America, and no significant developmental problems or other adverse events have been identified to date.⁹ We have no reason to believe that a significantly lower exposure would lead to adverse events not observed at therapeutic doses.

CONCLUSIONS

The results of this study, the first of its kind in Chagas disease, suggest that BNZ may be compatible with breast feeding due to limited drug transfer into breast milk and low potential infant exposure. This conclusion is further supported by the complete absence of ADRs attributable to BNZ in the breastfed infants. Our study provides, for the first time, support for continuation

of breast feeding during maternal treatment of Chagas disease, a practice that can potentially benefit many women and their breastfed infants in settings where maternal treatment during breast feeding may be advantageous.

Contributors FG-B: Conceptualised and designed the study, analysed data, drafted the initial manuscript, and approved the final manuscript as submitted. SM and GM: Recruited and followed patients, participated in the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. MEM, MB, LC, GB and GM: Developed and validated analytical methods, collected, prepared and analysed samples, analysed data, reviewed and revised the manuscript, and approved the final manuscript as submitted. JA: Conceptualised and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

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Competing interests FG-B is an associate researcher of the National Research Council (CONICET); JA is an independent researcher of the Buenos Aires City Health Research Council; LC and MEM received a scholarship, a 'Carrillo-Oñativia' award (Argentine National Research Commission 'Salud Investiga', Ministry of Health).

Ethics approval Research and teaching committee and bioethics committees of the Buenos Aires Children's Hospital 'Ricardo Gutierrez'.

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