Is use of nifurtimox for the treatment of Chagas disease compatible with breast feeding? A population pharmacokinetics analysis

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ABSTRACT

Introduction Women with Chagas disease receiving treatment with nifurtimox are discouraged from breast feeding. Many patients who would receive treatment with nifurtimox live in extreme poverty, have limited access to resources such as clean water and baby formula and may not have safe alternatives to breast milk.

Aim We aimed to estimate, using limited available pharmacokinetics data, potential infant exposure to nifurtimox through breast milk.

Methods Original nifurtimox plasma concentrations were obtained from published studies. Pharmacokinetic parameters were estimated using non-linear mixed-effect modelling with NONMEM V.VI. A total of 1000 nifurtimox plasma–concentration profiles were simulated and used to calculate the amount of drug that an infant would be exposed to, if breast fed 150 ml/kg/day.

Results Breast milk concentrations on the basis of peak plasma levels (1361 ng/ml) and milk–plasma ratio were estimated. We calculated infant nifurtimox exposure of a breastfed infant of a mother treated with this drug to be below 10% of the maternal weight-adjusted dose, even if milk–plasma ratio were overestimated. Simulation led to similar estimates.

Discussion Risk for significant infant exposure to nifurtimox through breast milk seems small and below the level of exposure of infants with Chagas disease receiving nifurtimox treatment. This potential degree of exposure may not justify discontinuation of breast feeding.

What is already known on this topic

- Nifurtimox is one of the only two drugs currently available for the treatment of Chagas disease, a chronic, debilitating parasitic disease endemic to Latin America. It is not known to what degree nifurtimox crosses into breast milk, but lactating women are strongly discouraged from using this drug and breast feeding.

What this study adds

- Transfer of nifurtimox into breast milk is expected to be limited and unlikely to lead to significant exposure of the breastfed infant.

Chagas disease is a parasitic disease endemic to Latin America caused by *Trypanosome cruzi* for which only two drugs, nifurtimox and benznidazole, are currently available.[1 2] It is a biphasic disease with a short acute phase and a prolonged chronic phase that eventually leads to the development of cardiac complications in up to 30% of infected patients.[2 3] Chagas disease affects predominantly poor, medically underserved people. It is estimated that there are currently about 15 million people infected in Latin America and over 15 000 deaths due to complications occur every year.[1 3 4]

Nifurtimox is used in the treatment of the acute or early chronic phase of Chagas disease. Women with Chagas disease receiving treatment with nifurtimox are discouraged from breast feeding due to lack of safety data.[5 6] Indeed, we could not identify any published study evaluating the degree of transfer of nifurtimox into breast milk, or studies of the pharmacokinetics of the drug in pregnant women or children. However, a few pharmacokinetics studies have been published in adult patients (table 1).[7–9]

Adult patients treated with nifurtimox for 60 days commonly develop significant adverse events to the drug, including anorexia, weight loss and neuropathy.[10] Unlike adult patients, infants and young children treated with nifurtimox only experience minor adverse events.[11–14] One study[14] described the treatment with nifurtimox of 102 infants from Northeast Argentina diagnosed with congenital Chagas disease. Six neonates had mild diarrhoea, and three developed mild rash. No severe adverse reactions were observed. Another study, also from Argentina,[11] described the treatment of 71 infants with nifurtimox. Data on adverse reactions were available on 62 of these infants, which included mild anorexia in 15 cases (a side effect commonly present and severe in adults), irritability in nine cases, vomiting in four cases and mild leucopenia and thrombocytopenia in three cases. None of these effects was severe enough to justify treatment discontinuation, and they all resolved spontaneously with no long-term sequelae. A third study from Chile[15] described the treatment with nifurtimox of 66 children (ages ranging from 1 month to 10 years old). No specific adverse reactions were described, but the authors mention that adverse reactions were mild and that none of the patients treated were excluded from the study because of adverse drug effects.[15]

Table 1 Summary of published pharmacokinetics studies of nifurtimox in adults

Published pharmacokinetics studies	N	Absorption rate (Ka (h^{-1})) mean (SD)	Volume of distribution (V/f (l)) mean (SD)	Clearance (Cl/f (l/h)) mean (SD)
González-Martin G *et al*[9]	7	0.973 (0.538)	529 (428)	99.7 (60.3)
Medenwald *et al*[8]	2	Not available	Not available	Not available
Paulos C *et al*[7]	7	0.767 (0.204)	755 (283)	193.4 (93.2)

We aimed to estimate, using limited available pharmacokinetics data, the potential degree of exposure to nifurtimox of an infant through breast milk of a mother receiving this drug in usual therapeutic doses.

METHODS

Original nifurtimox pharmacokinetics data were obtained from published studies.[7–9] Data used for modelling were only available from one study.[7] This study is in normal volunteers. The summary results of the study on renal failure patients[9] were used to confirm our estimates, but the original data were not available to include in the analysis. One study[8] reported data on two patients in the form of a plasma concentration–time graph, but no numerical data could be obtained from the paper. Pharmacokinetic parameters were estimated using non-linear mixed-effect modelling with NONMEM V.VI. An exponential distribution model was used to account for inter-individual variability.

Population pharmacokinetics parameters were calculated on the basis of published data,[7] assuming a one-compartment model with zero order absorption and lag.[8] Other competing models did not improve the fit of the data and were discarded. Visual inspection of the Visual Predictive Check (VPC) plot (figure 1) suggested good fit of the model to the data, as did the 'observed versus predicted' diagnostic graphs (figures 2 and 3). Parameter values obtained from the model are presented in table 2. The VPC graph (figure 1) was constructed by plotting the results of simulating, using the model-derived parameters, 1000 populations identical to the study population and overlapping the actual study population data onto the graph. VPC graphs provide a visual estimate of model misspecification[16] (eg, if most original data fall outside the range of the simulated data, the model does not reflect the original data very well). While a good fit (ie, most original data points falling within simulated range, such as in the case of our study) does not completely rule out model misspecification, it makes it less likely. 'Observed versus predicted' diagnostic graphs (figures 2 and 3) were constructed by plotting observed individual data versus data predicted by the model (for the same time and individual). The line of identity in these graphs marks the place where all points would fall if the model predicted exactly the original data. Any systematic deviation from this line would suggest model misspecification.

Simulations were conducted in NONMEM and R statistical language, V.2.8; confidence intervals for medians were calculated by the bootstrapping statistical method. Statistical calculations were performed in R statistical language, V.2.8.

Estimation of maximum exposure through milk using maximum reported plasma concentrations

The most commonly reported way of estimating infant drug exposure through breast milk is the calculation of daily

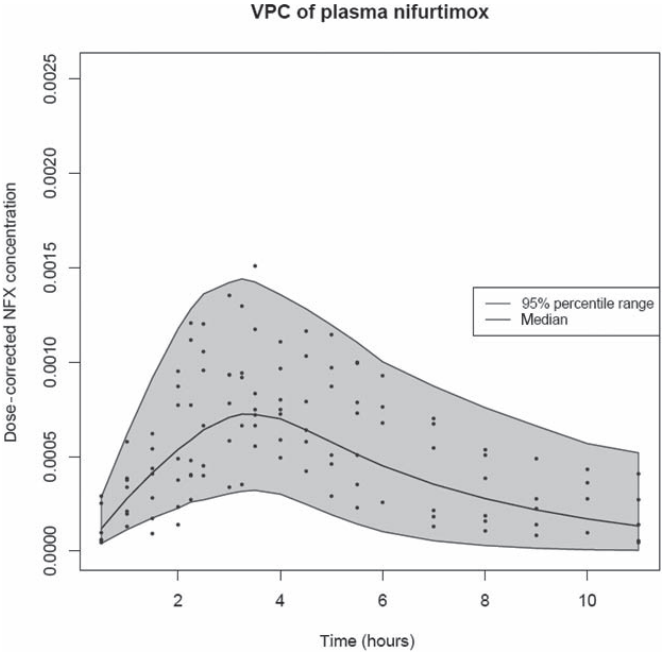

Figure 1 Visual Predictive Check (VPC) of the population pharmacokinetics model for nifurtimox, suggesting good fit of the model (95% percentile range – shaded area; median prediction – central line) to the data (closed circles) NFX, nifurtimox.

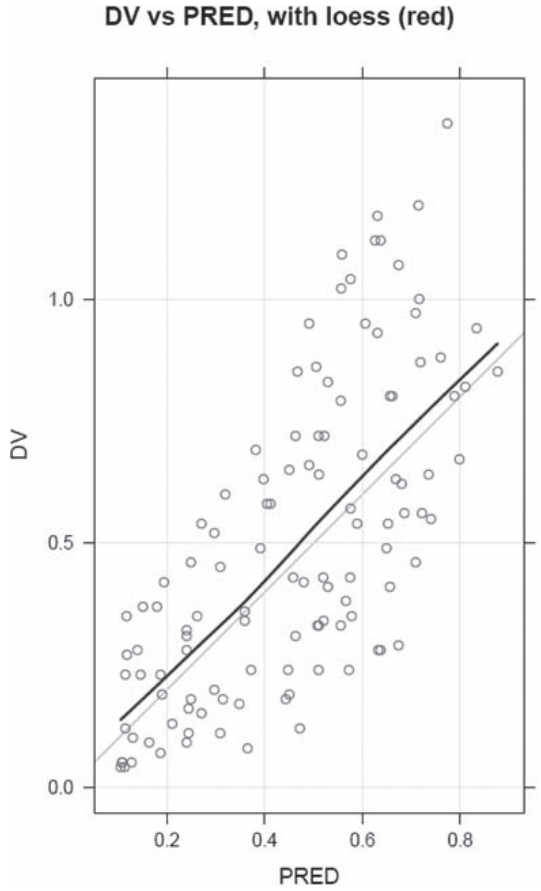

Figure 2 Observed (DV) versus model predicted (PRED) values diagnostic plot.

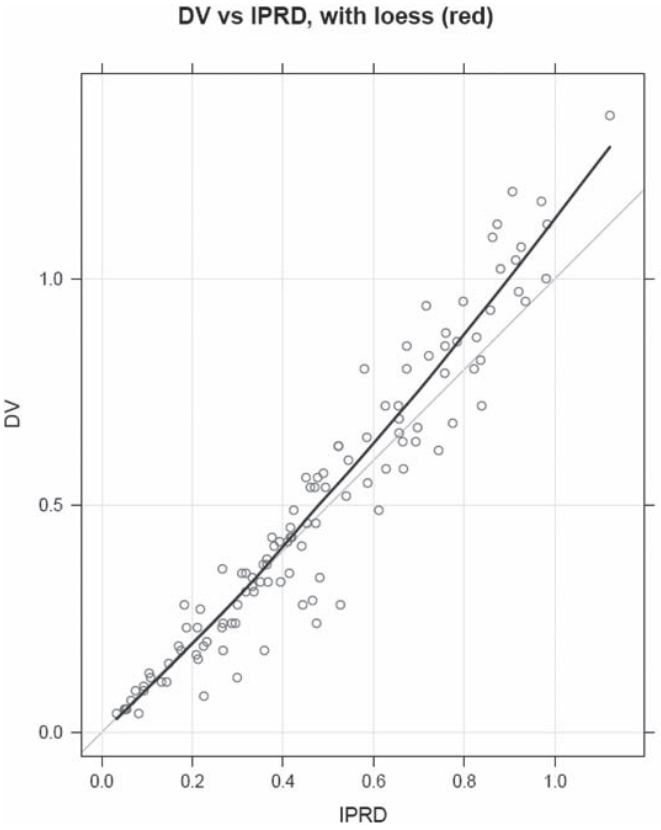

Figure 3 Observed (DV) versus individual predictions (IPRD) diagnostic plot.

exposure by taking the highest measured drug concentration in milk and multiplying it by 150 ml/kg to account for volume of milk ingested per day by the infant.[17] The highest published plasma concentration of nifurtimox (after a 15 mg/kg single dose)[7–9] was used to calculate, assuming an infant milk ingestion of 150 ml/kg/day,[18] and a milk–plasma ratio of 1.

Estimation of maximum exposure through milk using simulation

A population pharmacokinetics and simulation approach was used to estimate the potential limits to the exposure to nifurtimox via breast milk at the usual therapeutic dose of 5 mg/kg three times a day (15 mg/kg/day).

We calculated the population pharmacokinetics parameters using published data,[7] assuming a one-compartment model with zero order absorption and lag.[8] Other competing models did not improve the fit of the data and were discarded. Once the model parameters were obtained, 1000 plasma–concentration profiles of the drug at steady state (after chronic dosing with 15 mg/kg/day) were simulated using NONMEM. The simulated profiles were used to calculate the amount of drug that an infant would be exposed to, if breast fed 150 ml/kg/day divided in eight daily feedings (18.75 ml/feeding). The plasma concentrations at the estimated time of feeding were multiplied by the estimated volume of the feeding (ie, 18.75 ml), assuming a milk–plasma ratio of 1 (ie, breast milk concentrations of the drug would be the same as those in plasma). The total amount estimated to be ingested in each occasion was added to obtain the total daily dose ingested by each infant of each simulated mother.

Table 2 Population pharmacokinetics parameters of nifurtimox obtained with a one-compartment model with zero order absorption and lag

Nifurtimox model	Population estimate (THETA)	SE (%)	Variability (ETA)	Between-subject variability (%)
Lag in absorption (h)	0.15	23	0.16	40
Absorption constant (Tk0)	3.46	11	0.0562	23.7
Volume of distribution (V/f (l))	762	14	0.0819	28.6
Clearance (Cl/f (l/h))	191	18	0.182	43.8

Residual error 0.05 (22%).

Plasma concentrations of the 14th day after chronic dosing were chosen for the calculation to ensure steady-state concentrations in the simulated mothers.

RESULTS

Estimation of maximum exposure through milk using maximum reported plasma concentrations

Only three pharmacokinetic studies of nifurtimox have been published, all in adult patients.[7–9] The highest plasma concentration of nifurtimox observed in these studies after a 15 mg/kg single dose was 1361 ng/ml (1.361 mg/l). Assuming an infant milk ingestion of 150 ml/kg/day, and milk–plasma ratio of 1, a breastfed infant would receive a maximum of 0.2 mg/kg/day of nifurtimox through breast milk. This would represent 1.36% of the maternal weight-adjusted dose. This calculation assumes that this peak concentration in milk would remain stable throughout the day, which is clearly an overestimate.

Even a milk–plasma ratio of 6, such as reported for the chemically similar drug nitrofurantoin,[19] would not lead to an exposure beyond 10% the maternal weight-adjusted dose. It can also be anticipated that the currently used therapeutic dose (5 mg/kg three times a day) would lead to peak concentrations approximately one-third of those reported in the initial pharmacokinetics studies and, therefore, to lower exposures through breast milk (figure 4).

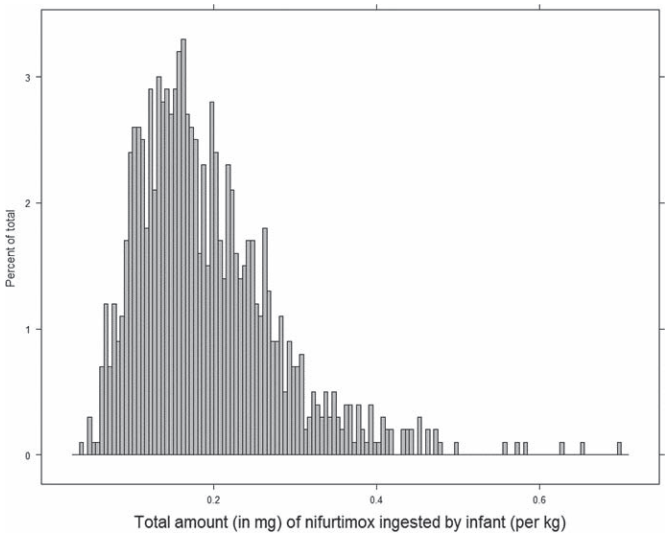

Figure 4 Simulation result (1000 mother–child pairs). Histogram of total amount (mg) ingested per kg through breast milk by baby breast fed by a 60 kg mother taking 900 mg of nifurtimox per day. Milk–plasma ratio=6.

Estimation of maximum exposure through milk using simulation

Simulation of 1000 nifurtimox plasma–concentration profiles assuming a milk–plasma ratio of 1 estimated a median daily dose to the infant of 0.19% of the maternal weight-adjusted dose.[17] The 99th percentile of the estimated dose in this group of simulated infants was 0.51% of the maternal weight-adjusted dose, with an upper 95% CI (for the 99th percentile) of 0.62%. Even if a milk–plasma ratio of 6 was assumed (as reported for nitrofurantoin[19]), the 99th percentile for the infant dose would be 3.1% of the maternal weight-adjusted dose (upper 95% CI for the 99th percentile=3.7%) (figure 5).

DISCUSSION

Using the traditional method[17] to estimate breast milk concentrations based on peak plasma levels and milk–plasma ratio, we estimated that the amount of nifurtimox to which a breastfed infant of a mother treated with the usual dose of 15 mg/kg/day would be exposed to is below 10% of the maternal weight-adjusted dose, even if drug transfer into milk (ie, milk–plasma ratio) is intentionally overestimated. It should also be kept in mind that neonatal Chagas disease is treated with doses similar to those used in adults (ie, 15 mg/kg/day).

However, this method is expected to grossly overestimate infant exposure through breast milk, as it assumes that peak concentration remains constant throughout the day. It also fails to take into account the pharmacokinetics variability inherent to human populations. Therefore, we have attempted to obtain a more accurate estimate of exposure that would incorporate current understanding of the pharmacokinetics of nifurtimox, as well as variability. We speculate that this model would better reflect the mean exposure in a population of infants and provide an estimate of the range of potential exposures in the same population.

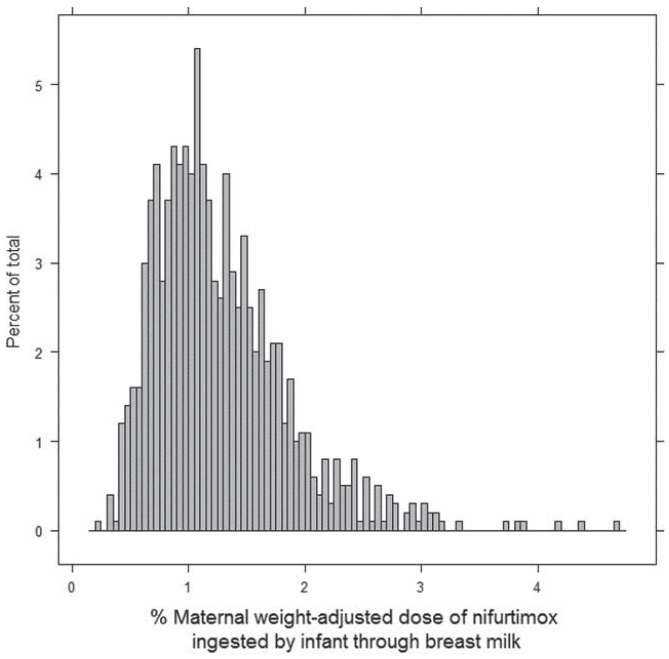

Figure 5 Simulation result (1000 mother–child pairs). Histogram of percentage of maternal weight-adjusted dose ingested through breast milk by infant breastfed by a 60 kg mother taking 900 mg of nifurtimox per day. Milk–plasma ratio=6.

Population pharmacokinetics modelling and simulation led to similar estimates and has the advantage of taking into account the full daily plasma–concentration profile of the drug. It also permits calculation of the 99th percentile of the simulated exposures which provides a higher degree of certainty that the results are not overly lax estimates. Simulation can be used to generate a large number of theoretical drug concentration profiles, which allows estimation of extreme values. It is somewhat reassuring that, even under these extreme assumptions, estimated infant exposure did not exceed 10% of the maternal weight-adjusted dose. Put in the context of usual infant therapeutic doses, breastfed infants would be exposed to no more than 10% of the commonly used neonatal dose (15 mg/kg/day three times a day). It should be noted, however, that simulation is based on existing data obtained from a limited number of adult patients and that simulations from such a reduced sample cannot be expected to be very accurate. On the other hand, even after applying a relatively large margin of safety (ie, assuming a high milk–plasma ratio of 6 and using the 99th percentile of the estimate for final calculations), our results still did not suggest a risk for significant infant exposure.

Application of well-described models that attempt to predict drug transfer into breast milk on the basis of its physicochemical properties[20 21] would produce an estimate for milk–plasma ratio for nifurtimox similar to that of nitrofurantoin, 0.28.[19] However, experimental determination of nitrofurantoin transfer into breast milk showed an unexpectedly higher milk–plasma ratio of 6.[19] This unexpected result is likely due to active secretion of nitrofurantoin into milk by breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter protein that seems to play an important role in the pharmacokinetics of many medications, and is highly expressed in breast tissue.[22] Structural similarities between nitrofurantoin and nifurtimox suggest that the latter could also be a substrate of BCRP, which could mean higher milk–plasma ratios than anticipated by its physicochemical characteristics alone. However, the role of BCRP in the pharmacokinetics of nifurtimox remains unexplored.

Most of the acute infections in Chagas disease occur in children or young adults. Early pharmacological treatment is effective and can prevent progression into the chronic stage. Once patients reach the chronic stage medications have limited effectiveness, and severe sequelae (ie, irreversible heart disease) ensue in 30% of patients.[1] Millions of people live in the endemic areas for Chagas disease, making it likely that many young women would require treatment with nifurtimox while breast feeding. Many of the patients who would receive treatment with nifurtimox live in extreme poverty.[1] In this setting, access to resources such as clean water and baby formula is far from ideal, and, given current recommendations to avoid NFX during lactation, a breastfeeding woman requiring treatment would be faced with the choice of being treated for a life-threatening disease, or breast feeding her child. If she chooses to receive the treatment, she may lack the resources to provide appropriate alternative food for her baby. We believe that our results can help develop a more balanced risk–benefit evaluation of this situation.

A large amount of data has also been collected in the last decade to support the effectiveness and safety of nifurtimox in the treatment of African Trypanosomiasis (sleeping sickness). We expect that our findings would be applicable to this devastating disease as well.[23]

CONCLUSION

The recommendation to avoid breast feeding while on nifurtimox lacks support when the data available are taken into account. The potential degree of exposure through breast milk is likely to be small. When the vast body of evidence supporting the benefits of breast feeding is taken into account, the risk–benefit balance clearly supports continuation of breast feeding in this context.

An important limitation of this study is lack of experimental data from breastfeeding women. We acknowledge that no study has been performed to measure breast milk concentrations of nifurtimox to date and that clinical validation of our theoretical model is required before a general recommendation can be made.

Nonetheless, there is ample evidence suggesting that breast feeding provides large benefits, in particular in the context of the underserviced, impoverished populations where Chagas disease thrives. The risks of delaying treatment with nifurtimox or, even worse, discontinuing breast feeding in the face of nifurtimox treatment should be strongly considered in particular given the lack of evidence to support transfer of nifurtimox to any significant level into breast milk. Discontinuation of breast feeding is not without risks, and the decision to stop breast feeding should be carefully weighed against the risks, including potential impact on infant health of maternal milk deprivation.

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