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Pediatric Clinical Pharmacology Studies in Chagas Disease

Focus on Argentina

Facundo Garcia-Bournissen,[1] *Jaime Altcheh*,[2] *Norberto Giglio*,[3] *Guido Mastrantonio*,[4] *Carlos Omar Della Védova*[4] and *Gideon Koren*[1]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
2 Division of Parasitology, Hospital de Niños 'Ricardo Gutierrez' de Buenos Aires, Buenos Aires, Argentina
3 Division of Epidemiology, Hospital de Niños 'Ricardo Gutierrez' de Buenos Aires, Buenos Aires, Argentina
4 LaSeISiC (UNLP-CIC-CONICET), Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Buenos Aires, Argentina

Abstract

Chagas disease is a neglected parasitic disease endemic in the Americas. It mainly affects impoverished populations and the acute phase of the infection mostly affects children. Many cases have also been detected in nonendemic countries as a result of recent migratory trends. The chronic phase is relatively asymptomatic, but 30% of patients with chronic infection eventually develop cardiac and digestive complications that commonly lead to death or disability. Only two drugs are available for the treatment of Chagas disease, benznidazole and nifurtimox. These drugs have been shown to be effective in the treatment of both acute and early chronic phases in children, but the pharmacokinetics of these drugs have never been studied in this population. We have set out to conduct a pharmacokinetics study of benznidazole in a pediatric population with Chagas disease. The results of this study are expected to allow better estimation of the optimal doses and schedule of pharmacotherapy for Chagas disease in children.

Chagas disease is one of the most neglected diseases in the world. It is a zoonosis caused by infection with the parasite *Trypanosoma cruzi*. The geographic distribution of this disease is wide, from southern USA to southern Argentina, with endemic characteristics seen from the north of Mexico to the north of Argentina.[1] Many cases have been detected in nonendemic countries in the last decade due to recent migratory trends and improvements in screening techniques.[2]

There are currently about 15 million people infected in Latin America; approximately 200 000 new cases and over 15 000 deaths as a result of complications of the disease occur every year.[1,3] *T. cruzi* can be transmitted by hematophagous arthropod vectors (triatomines), blood transfusions,[4] or vertical transmission (i.e. mother to child).[5,6] Most of the new infections occur in children, either by vector or vertical transmission,[7] with an estimated mortality of approximately 5%, mainly as a result of myocarditis and meningoencephalitis.[1,7]

The acute phase of the disease lasts approximately 4 weeks, and is followed by a chronic asymptomatic stage that eventually leads to irreversible heart disease in up to 30% of infected patients many years after the initial infection.[1,7] The chronic stage is when most of the mortality and disability associated with Chagas disease occurs. The most common complications observed in this phase include dilated cardiomyopathy, arrhythmias, heart failure, sudden death, megaesophagus, and megacolon.[1,7]

Estimated economic costs associated with Chagas disease in Latin America are estimated to be in the order of $US6 billion per year. The majority of the costs are associated with healthcare expenses and with the loss of work productivity in the young population affected.[3]

In Argentina, where 89% of the population lives in urban areas, in particular in or around the country's capital Buenos Aires, most of the patients infected with Chagas disease live in an urban setting. The prevalence of Chagas disease in children and women

attending primary care centers in Buenos Aires has been estimated to be about 2%.[8] Most new infections in urban areas are due to vertical transmission and occasionally due to blood transfusions.[5]

Pharmacology, Efficacy, and Tolerability of Treatments for Chagas Disease

Pharmacotherapy of Chagas Disease

There are only two drugs currently available for the treatment of Chagas disease, nifurtimox and benznidazole.[1]

Benznidazole, a nitroimidazole compound, was developed almost 40 years ago.[9] The mechanism of action of benznidazole is still not clear, but it has been shown to induce reductive stress leading to covalent modification of proteins and other macromolecules in *T. cruzi*.[1,10] Benznidazole, and possibly its metabolites, induces the production of free radicals that can damage the DNA of the parasite, as well as inhibit RNA and protein synthesis.[9,11]

Benznidazole followed one-compartment model pharmacokinetics in healthy men who volunteered to receive oral benznidazole 100 mg.[12-14] The peak plasma concentration of 2.2–2.8 mg/L was observed 3–4 hours post dose. The estimated elimination half life ($t_{1/2}$) was 12 hours, and the apparent volume of distribution (Vd) was 0.56 L/kg.[13] In a study of multiple doses of benznidazole in adults with Chagas disease,[14] doses of 7 mg/kg produced overall plasma concentrations similar to those estimated from the pharmacokinetic parameters in the previous study in healthy volunteers.[13] Benznidazole is eliminated by the liver, with <20% of the drug excreted unchanged by the kidney. There are virtually no studies on the metabolism of benznidazole in humans, and very little information is available from animal studies.[10,15-20]

Nifurtimox leads to the production of free radicals and reductive damage of parasite cellular components such as proteins and nucleic acids. Inhibition of the enzyme tripanotionine reductase is believed to also play a role in the parasiticide action of nifurtimox through inhibition of tripanotionine metabolism; tripanotionine is a molecule that is important for the detoxification of reactive intermediate products of the metabolism of the parasite.[9-11] Similar to benznidazole, the pharmacokinetics of nifurtimox seem to follow a one-compartment model.[21,22] Pharmacokinetics studies on this drug published to date were carried out on adult healthy volunteers and in patients with chronic renal failure. Healthy adults who received a dose of oral nifurtimox 15 mg/kg had a median peak plasma concentration of 0.7 mg/L that occurred between 3 and 4 hours after administration. The estimated $t_{1/2}$ of the drug was 3.5 hours and the Vd was 529 L.[21] Nifurtimox is eliminated mainly by the liver, with <1% leaving the body unchanged.[23,24] It has wide tissue distribution, as reflected by the large Vd. Studies on the mechanisms of biotransformation of nifurtimox in the liver suggest that cytochrome P450 enzymes are likely to be responsible for most of the metabolism.[23-25]

Clinical Trials in Pediatric Chagas Disease

A small number of pediatric clinical trials in Chagas disease have been conducted, which have consistently shown that the treatment of children in the acute or in the indeterminate (quiescent) phase leads to a cure.[26-34] These results have prompted the release of guidelines for the pharmacologic treatment of pediatric Chagas disease indicating that all children <15 years of age with Chagas disease should be treated for 60 days with one of the two available drugs, irrespective of the phase of the infection.[35,36]

Pharmacologic treatment of Chagas disease in the early chronic phase is effective and carries a high cure rate.[3,26-33,35,37-40] It was previously thought that treatment of adults in the chronic phase was not effective, but this concept has been challenged by small clinical trials suggesting some degree of clinical improvement. Trials to evaluate the effectiveness of long-term treatment in reducing complications in adult patients in the chronic phase are currently underway.[41,42]

In spite of the evidence of the effectiveness of benznidazole and nifurtimox in children, the information available on the pharmacokinetics and pharmacodynamics of these drugs in children is extremely limited.[35] To date, dosing decisions in children have been made on the basis of the scarce data available from the adult population, and have not taken into account any pharmacokinetic characteristics of these drugs in children. To make matters worse, no appropriate pediatric formulations (e.g. liquid formulation) are available, which all too frequently forces healthcare providers to resort to pill fractionation, a methodology fraught with difficulties and risks.[43-45]

The most commonly observed adverse drug reactions are very similar for both benznidazole and nifurtimox in pediatrics and include nausea, anorexia, headache, gastrointestinal discomfort, and arthralgias.[26] Maculopapular rash and pruritus are also relatively frequent, and are a common reason for treatment discontinuation. More severe reactions associated with benznidazole treatment, such as severe cutaneous reactions, peripheral neuropathy, and granulocytopenia, are rarely observed in children, but can be relatively frequent in adults.[26] It is not currently known whether there is a correlation between these adverse reactions and drug plasma levels, mainly because there is virtually no information on plasma levels in children. Nevertheless, some adverse drug reactions associated with these drugs, such as peripheral polyneuropathy and gastrointestinal complications, seem to be dose-dependent

which would suggest a correlation to plasma levels. Peripheral polyneuropathy, in particular, is a frequent observation in the adult population (about 20% of treated patients), but is rare in children.[29,46,47] Its incidence and severity in adults are dose-dependent; this has been confirmed in experiments in dogs.[47,48]

In response to this dearth of information on benznidazole and nifurtimox in the pediatric population, the Scientific Working Group on Chagas Disease, Special Programme for Research and Training in Tropical Diseases (TDR), WHO/Pan American Health Organization (PAHO) has signaled the study of the pharmacokinetics of these agents in children as a research priority.[49]

Pediatric Pharmacology Studies

Pharmacokinetic studies have traditionally involved a limited number of patients, usually adult healthy volunteers. The pharmacokinetic profile of the studied drug would usually be characterized extensively in each individual participant, which requires a large number of samples to be obtained. The requirement for extensive sampling makes these studies very difficult to perform in pediatric populations due to ethical and logistical limitations (e.g. blood volume restrictions, inordinate number of required punctures).

In the last few decades, a new approach to pharmacokinetics, population pharmacokinetics, has gained momentum as the method of choice when studying vulnerable populations such as children. This method changes the focus away from the complete estimation of the pharmacokinetic parameters in each individual participant towards the estimation of the parameters (and their variability) in the whole population. In order to estimate the pharmacokinetics of a drug from a population perspective, a larger number of individuals is required to participate, but the amount of samples per individual is greatly reduced (to as few as two samples in some study designs).[50-55] This milder burden on the individual patient makes population pharmacokinetics the ideal choice for studies in children. The US FDA and the European Medicines Agency recommend this method as the standard for pharmacokinetic studies in children.[56-59]

Study of the Pharmacokinetics of Benznidazole in Children with Chagas Disease in Buenos Aires, Argentina

Given the absolute absence of data on the pharmacokinetics of benznidazole in the pediatric population, we set out to perform a population pharmacokinetics study in children receiving this drug for the treatment of Chagas disease. Benznidazole was chosen over nifurtimox because of accessibility issues; benznidazole was relatively easier to obtain in Buenos Aires at the time that the study was started.

The study[60] was designed as an observational, prospective, population pharmacokinetics study, enrolling children with Chagas disease of both sexes who were 2–12 years of age and eligible for treatment with benznidazole, as per current treatment protocols.[5,26,27,29] The diagnostic criteria of Chagas disease required for patient inclusion in the study includes at least two positive serologic tests for *T. cruzi* infection (ELISA, hemagglutination, and particle agglutination tests). Informed consent signed by the caregivers and the assent of the patient is required. Patients with a history of hypersensitivity to benznidazole or any of the drug excipients, immunocompromised patients, and patients with altered hepatic or renal function are excluded from participation.

Patient recruitment is currently taking place at the Parasitology Division, Children's Hospital 'R Gutierrez' of Buenos Aires, Buenos Aires, Argentina, where these patients are routinely treated and followed up. Recruitment is carried out by a team of pediatric investigators headed by Dr Jaime Altcheh, the principal investigator. A total of 50 patients will be enrolled in the study.

The patients will receive, as per the routine treatment protocol of Chagas disease, oral benznidazole (RADANIL®, Roche, Buenos Aires, Buenos Aires, Argentina) 5–8 mg/kg/day twice daily for 60 days. Treatment will occur in an outpatient setting and will follow the usual management protocol for children with Chagas disease. Benznidazole is provided free of charge by the National Agency of Medications, Food, and Technology (ANMAT), National Ministry of Health, Buenos Aires, Argentina. Benznidazole is extracted and measured (by high-performance liquid chromatography) according to published protocols.[17-21]

We expect the recruitment phase of the study to take an estimated 24 months. The study is being conducted according to the guidelines of the International Conference on Harmonization (ICH6), Good Clinical Practice guidelines (GCP), the declaration of Helsinki, the UNICEF convention on the rights of children, and the regulations of the ANMAT.

Conclusion

Chagas disease is a chronic infection that is usually acquired in infancy but that leads to deleterious consequences for the patient and society many years after the initial presentation. Many aspects of the treatment of this disease still remain unstudied, in particular the optimal doses and treatment schedules. In spite of the currently available drugs (benznidazole and nifurtimox) being effective in children, there is still a dire need for new, safer drugs for the acute phase and drugs that are effective for the late chronic phase of the disease in both children and adults. In spite of the public health and economic implications of this disease for Latin America, very few

efforts are being directed towards the development of new medications.

We have attempted to carry out the first pharmacokinetics study of benznidazole in the pediatric population. We expect that the results of this study will lead to a better understanding of, and eventually significant improvements in, the pharmacotherapy of Chagas disease in children.

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Correspondence: Dr *Facundo Garcia-Bournissen*, Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, University of Toronto, 555 University Ave, Black Wing, 8th floor, Room 8232, Toronto, ON M5G 1X8, Canada.

E-mail: Facundo.garciabournissen@sickkids.ca