# Tolerance of Benznidazole in a United States Chagas Disease Clinic

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**The US–based Center of Excellence for Chagas Disease performed an observational study on the safety and tolerance of benznidazole 5 mg/kg/day for 60 days in 30 adults with chronic Chagas disease. The side-effect profile was suboptimal, including 5 cases of debilitating neuropathy and an unusually high angioedema rate.**

***Keywords.*** Chagas disease; trypanosomiasis; benznidazole; United States; drug tolerance.

Chagas disease, primarily endemic to Latin America, afflicts 8–10 million people worldwide [1]. The often untreated acute protozoan illness evolves to a chronic clinically silent (indeterminate) phase; 20%–30% of cases will progress to cardiac or gastrointestinal disease after years to decades [2]. Through immigration, the United States has become the seventh largest chagasic population in the world, with >300 000 affected persons [3]. Ten percent to 15% have cardiomyopathy [3], and the remainder carry a substantial risk of disease progression [4], contributing to an annual economic burden of >$100 million [5].

Treatment of adults in the chronic phase has been evidenced to acutely eliminate polymerase chain reaction positivity, reduce long-term seropositivity, slow the progression of cardiomyopathy, and possibly decrease maternal-to-child and blood donor–related transmission [6–9]. However, the significant side-effect profile of the recommended chemotherapeutics will continue to obscure the risk-benefit ratio of treatment until large prospective trials that are under way can further refine the utility of therapy [10]. The 2007 US guidelines [11] recommend offering treatment to all chronic chagasic patients aged 19–50 in the absence of pregnancy, hepatic or renal failure, or advanced cardiomyopathy, and favor benznidazole (over the less well-tolerated nifurtimox) at 5–7 mg/kg/day in 2 divided doses for 60 days [11], although there remain inadequate data to guide optimal dosing.

The Center of Excellence for Chagas Disease (CECD) at the Olive View–UCLA Medical Center is the first dedicated Chagas disease clinic in the United States to systematically review and treat Chagas disease. This study aimed to evaluate the tolerance of benznidazole in an adult US cohort to better understand the barriers to completing therapy and to refine our treatment standards in this population.

## MATERIALS AND METHODS

### Study Design, Setting, and Population

CECD is a public university–affiliated clinic that provides care to patients regardless of insurance status or ability to pay. There were 2 446 000 foreign-born Hispanics [12] in Los Angeles County during the study period. A panel of nearly 300 patients had been acquired through in-hospital and community outreach screening, routine blood bank referrals, and solicitation of chagasic patient family members. This retrospective observational study reviews the initial 30 consecutive chagasic patients treated with benznidazole (February 2011 through July 2013) since it last became available from the Centers for Disease Control and Prevention (CDC) through a Food and Drug Administration protocol. Nifurtimox had previously been the single available agent.

Diagnosis was confirmed by 2 CDC serological tests, using an immunofluorescent antibody titer ≥1:32, an enzyme immunoassay, and, as a tiebreaker, a trypomastigote excreted-secreted antigens Western blot. Patients aged ≥18 years were invited to undergo clinical evaluation including disease staging and elicitation of contraindications to medical therapy. Cardiomyopathy was characterized by electrocardiography, echocardiography, and cardiac magnetic resonance imaging. Patients were excluded from receiving benznidazole for Kuschnir grade III cardiomyopathy (Chagas-associated congestive heart failure) [13], pregnancy, severe hepatic or renal insufficiency, or inability to state commitment to follow-up appointments. Patients aged >50 years were factored on a case-by-case basis. Patients eligible for benznidazole therapy received risk-benefit consultation and signed informed consent prior to treatment.

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Dosing of benznidazole (manufactured by Laboratório Farmacêutico de Pernambuco [LAFEPE]) consisted of 5 mg/kg/day in 2 divided doses for 60 days, initiated at half-dose and up-titrated to the full dose over the first 4 days. Clinical evaluation included systematized history, symptom surveillance, physical examination, and serum analysis (chemistries, liver function tests, and complete blood count) at 2, 4, 6, and 8 weeks, 1 month after therapy completion, and at 1 year. Treatment terminations were determined by the patient and/or the CECD program director.

### Data Collection

A standardized medical records abstraction instrument was used to gather adverse event (AE) data that had been prospectively recorded in a format adherent to the National Institutes of Health Common Terminology Criteria for Adverse Events, version 4.0 [14]. Institutional review board exemption for medical records review was obtained through the Olive View–UCLA Education and Research Institute.

### Statistical Methods

Statistical analysis was performed using SAS version 9.3.1 (Cary, North Carolina). Bivariate analyses were conducted using the Mann–Whitney *U* test, Student *t* test, and Fisher exact test, as appropriate, to calculate *P* values. Variables were considered significant at the $\alpha = .05$ level.

## RESULTS

Thirty patients received benznidazole: mean age was 42 years (range, 17–67 years), 18 (60%) were female, 10 (33%) had cardiomyopathy, and 2 (7%) had indigestion issues too minor to alter clinical management. Twelve patents (40%) were from each Mexico and El Salvador, 1 (3%) was from Colombia, another from Nicaragua, and 2 (7%) were born in the United States without clear epidemiological exposure. Four patients eligible to receive benznidazole refused therapy. No patients were lost to follow-up.

All 30 patients had AEs: 28/30 (93%) experienced >1 AE; 12 had severe AEs, none life threatening (Table 1). Rash principally involved the classically described maculopapular eruption occurring within the first 2 weeks and resolving spontaneously within 2 weeks. There was a trend toward an association between rash and higher mean weight (81 kg vs 72 kg; $P = .054$), body mass index (29.8 kg/m$^2$ vs 27.4 kg/m$^2$; $P = .24$), and, therefore, benznidazole total dose. There were no cases of Stevens–Johnson syndrome. Facial angioedema generally developed within the first 2 weeks of therapy, always in the setting of dermal hypersensitivity (24% [4/17]), progressing invariably over hours with symmetrical swelling of the eyelids and lips (Figure 1). Two cases categorized as angioedema were limited to peripherally localized swelling—1 case involving the hand, and another the shoulder. All cases of angioedema were observed by providers, yet reported by the patients to be spontaneously improving by the time of clinical contact. No dyspnea or wheezing was observed. There was a trend toward an association with angioedema and higher mean weight (83 kg and 75 kg, respectively; $P = .22$). No association could be attributed to either of the 2 benznidazole lot numbers (L09070538, L11121421) in use.

Peripheral sensory neuropathy occurred only in those patients who completed the 60-day regimen, occurring within the last 2 weeks of therapy. Neuropathies were clinically diagnosed and were typically mild with symptoms of formication, numbness, pain, and dysgeusia. However, painful neuropathy limited instrumental activities of daily living in 3 cases and activities of daily living in 2 others. Neuropathy resolved except in 3 patients exhibiting only slow, progressive improvement (lasting up to 3.5 years at the time of manuscript submission).

**Table 1. Adverse Events (N = 30)**

| Outcome | No. of Patients (%) | No. of Patients With Moderate or Severe AE[a] |
|---|---|---|
| Any adverse event | 30 (100%) | |
| Total discontinued | 9 (30%) | |
| Discontinued secondary to AE | 6 (20%) | |
| Rash | 16 (53%) | 8 (27%) |
| Headache | 15 (50%) | |
| Anorexia | 15 (50%) | |
| Neuropathy | 14 (47%) | 5 (17%) |
| Insomnia | 10 (33%) | 2 (7%) |
| Nausea | 10 (33%) | |
| Angioedema[b] | 6 (20%) | 6 (20%) |
| Abnormal liver function tests | 4 (13%) | |
| Leukopenia | 1 (3%) | |

Twenty-one patients (70%) completed therapy. Six patients (20%) discontinued as a direct result of treatment-related AEs: 4 (13%) due to facial angioedema, 1 (3%) due to rash without angioedema, and 1 (3%) due to mild transaminitis near the end of therapy (peak alanine aminotransferase level, 4 IU/L). Treatment interruption was elected in 1 patient for 1 week, which was prompted by rash and transient angioedema of the hand; these symptoms did not return after resuming therapy and extending treatment duration to complete the 60-day course. Non-therapy-related treatment discontinuations included 1 patient with a urinary tract infection at 4 weeks, 1 patient with incidental development of lichenoid keratosis on his chest wall at 7 weeks, and 1 patient who became overwhelmed by concurrent dental caries at 7 weeks. All occurrences of transaminitis (4/30 [13%]) remained <5 times the upper limit of normal. One patient developed leukopenia with neutropenia after 2 weeks of therapy, which improved after angioedema prompted therapy discontinuation.

Abbreviation: AE, adverse event.

[a] Common Terminology Criteria for AEs.

[b] Severe by definition.

## DISCUSSION

Our observation of a relatively high AE-related discontinuation rate [15] was notable for an unusual frequency of angioedema,

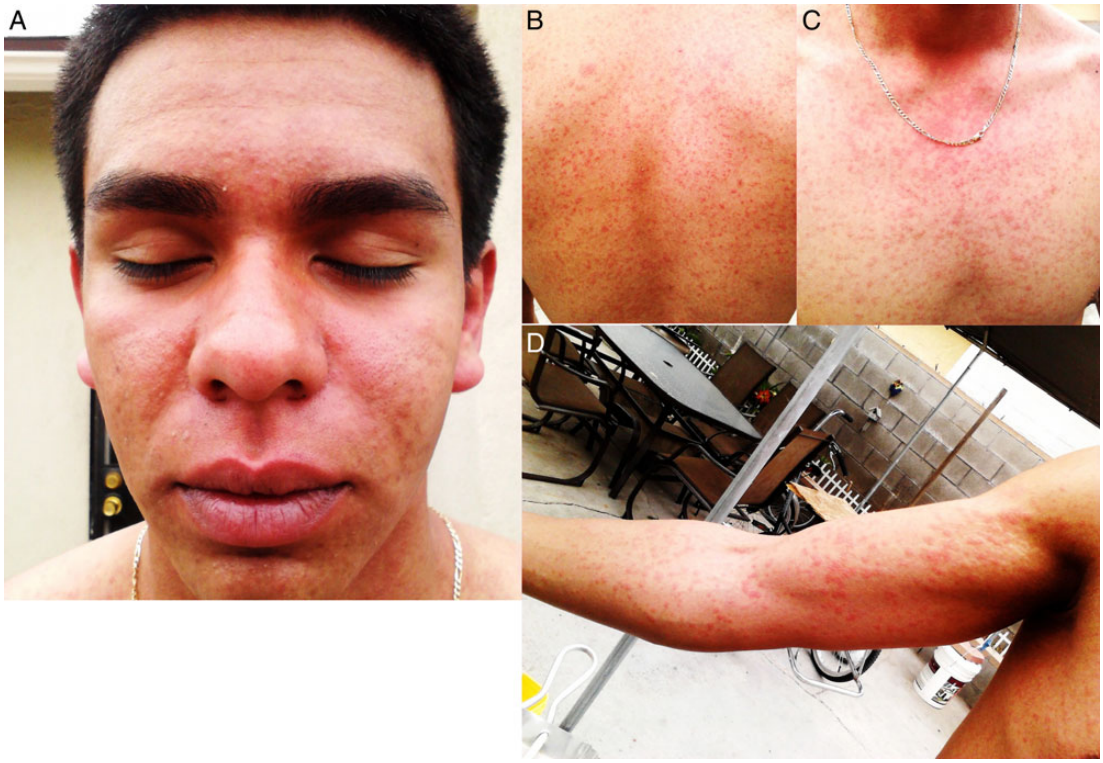


**Figure 1.** Case of angioedema and rash. Patient's face (*A*), back (*B*), chest (*C*), and arm (*D*) are featured. The patient presented to the emergency department within 2 weeks of treatment initiation with acute onset of symmetrical labial and periorbital swelling with "eyes swollen shut." Photographs were taken 48 hours after last benznidazole dose with interval improvement in facial edema. The patient provided consent to allow publication of photo without anonymity.

an otherwise rare AE [9]. The abrupt onset of localized edema represents a distinct clinical entity from the rash-associated edema conventionally described [15]. The root cause remains speculative and cannot be readily attributed to differences in lot number, dosing regimen, genetic predisposition, or diet. Although LAFEPE produces benznidazole consumed in select Latin American nations without similar reported angioedema frequency, monitoring of the aforementioned lot numbers is warranted.

Our cohort is clinically distinct from other studies in nonendemic countries, in that European cohorts are principally comprised of Bolivian immigrants [4] treated with benznidazole from a different manufacturer [16], and the clinical manifestations and drug susceptibility of *Trypanosoma cruzi* vary regionally [17].

We observed that rash and angioedema may have correlated with higher doses. Notably, children are successfully treated with comparable (mg/kg) dosing strategies and experience minimal AEs [18], suggesting that adults have a decreased weight-corrected clearance of benznidazole and, therefore, a higher serum half-life. As pharmacokinetic studies to better understand AE and clinical outcome profiles are lacking [19], avoidance of high doses of benznidazole may be wise. We adopted a strategy widely utilized in Latin America; the total daily benznidazole dose is capped at 300 mg/day with extension of therapy past 60 days to complete the equivalent cumulative dose [20].

Rash is common and typically the principal provocation for treatment interruption, yet, apart from cases of concomitant facial angioedema, severe rash did not necessarily entail therapy interruption, and could be temporized with antihistamines or steroids.

Neuropathy was commonly observed and, in 2 cases, limited ambulation and manual dexterity, resulting in prolonged unemployment. Importantly, a 30-day course of therapy has been evidenced to decrease the progression of cardiomyopathy and possibly decrease mortality while evading the cumulative toxic neuropathy found typically at the end of a 60-day regimen [6]. Until the benefit of a more prolonged therapy is demonstrated, we believe that symptoms of neuropathy should prompt immediate treatment interruption.

This study demonstrates a significant yet non-life-threatening side-effect profile of benznidazole in an adult US population. The suboptimal drug tolerance of benznidazole and nifurtimox in adults needs to be carefully considered in the decision to treat chronic Chagas disease while awaiting results of the large

prospective multicenter Benznidazole Evaluation for Interrupting Trypanosomiasis trial, which is expected to provide more clarity on the merits of universal treatment [10]. Pharmacokinetic profiling and optimization of dosing strategies while limiting hypersensitivity-mediated and neuropathic AEs will be critical to provide safe clinical management to patients with this infection that is increasingly recognized in nonendemic nations.

## Notes

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***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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