Adverse Events After the Use of Benznidazole in Infants and Children With Chagas Disease

WHAT'S KNOWN ON THIS SUBJECT: Treatment of Chagas disease with benznidazole in adults leads to a high incidence of severe drug reactions. However, benznidazole seems to lead to less frequent (and less severe) ADRs in children, but there are scarce data on the subject.

WHAT THIS STUDY ADDS: We describe a cohort of children with Chagas disease treated with benznidazole. A lower incidence of ADRs was observed in smaller children compared with older children and adults. All ADRs observed were mild, and treatment response was excellent.

abstract

BACKGROUND: Chagas disease is caused by infection with *Trypanosoma cruzi*. In adults, treatment with benznidazole is associated with a high incidence of adverse drug reactions (ADRs). However, in infants and children, treatment with benznidazole seems associated with a lower incidence and decreased severity of ADRs, but these effects have not been clearly characterized.

OBJECTIVE: We aimed to describe ADRs observed in infants and children treated with benznidazole.

PATIENTS AND METHODS: We conducted a prospective cohort study of infants and children in Argentina with Chagas disease treated with benznidazole.

RESULTS: A total of 107 infants and children diagnosed with asymptomatic Chagas disease (mean age: 6.9 years) were enrolled in the study. Sixty-two events (in 44 children) were considered benznidazole related. Mean ADR duration was 8.2 days. ADRs were mild (80.6%), moderate (16%), or severe (3.2%). Most (77.3%) ADRs were in children older than 7 years. Skin was the organ with the highest incidence of ADRs (21%), followed by the central nervous system (9%) and the gastrointestinal tract (8.5%). Also, the ADR rate was lower in infants and toddlers compared with older children (18% vs 53%) ($P < .001$).

CONCLUSIONS: Treatment with benznidazole was well tolerated in children. Most ADRs were mild and did not require treatment suspension. A strong association was observed between ADR incidence and patient age, and most ADRs occurred in children older than 7 years. We believe that anxiety over potential severe ADRs in children with Chagas disease is not justified and should not be an obstacle to using benznidazole. *Pediatrics* 2011;127:e212–e218

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KEY WORDS

infant, children, Chagas disease, congenital, benznidazole, adverse events, pediatric pharmacology

ABBREVIATIONS

ADR—adverse drug reaction
CI—confidence interval
IQR—interquartile range
CNS—central nervous system

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Chagas disease is a devastating disease caused by infection with the parasite *Trypanosoma cruzi*[1,2] and currently afflicts over 7 million people in the Americas.[1,3–5] Chagas disease has expanded to virtually all the countries of the world via immigration, with many cases reported in Europe and North America.[4]

Most of the infections take place in children, by vector or congenital transmission, with other modes of infection such as blood transfusion, organ transplants, and oral route being less frequent. Most patients have mild symptoms or are asymptomatic.[1] The initial acute phase is followed by a chronic asymptomatic stage that eventually leads to irreversible heart disease many years later in up to 30% of the infected patients.[6,7] The majority of the deaths attributed to cardiac complications (>7000 deaths per year) occur in adults infected in childhood.[5,6,8,9]

Pharmacologic treatment in the acute stage can cure the disease and prevent progression.[7,10–21] However, only 2 drugs currently are available, nifurtimox and benznidazole,[21] both with similar effectiveness.[22] Unfortunately, appropriate pediatric formulations are not available, and administration of the medication to children often requires tablet fractionation.

Treatment with benznidazole in adults is associated with a more than 30% incidence of adverse drug reactions (ADRs), including neuropathy and severe dermatological and gastrointestinal symptoms, and over 20% of treatments are interrupted.[23] Children seem to tolerate these treatments better, but these observations have not been clearly characterized.[1] The pharmacological basis for the differences in incidence and severity of ADRs between children and adults remain to be studied.

Regardless of Chagas disease treatment guidelines[1,8] indicating that all infected children younger than 14 years should be treated, and failure to do so could be considered malpractice, many physicians and patients defer or refuse treatment because of anxiety over potential ADRs.[24] We aimed to describe ADRs observed in a prospective cohort of infants and children with Chagas disease who were treated with benznidazole.

PATIENTS AND METHODS

We conducted a prospective study of a cohort of infants and children with Chagas disease treated with benznidazole between September 2003 and October 2007. Treatment was open label for 60 days, with 3 years of follow-up.

Infants and children diagnosed at the Parasitology and Chagas Service at the Children's Hospital "Ricardo Gutierrez" of Buenos Aires were evaluated. Subjects meeting all of the following criteria were considered for inclusion: were less than 20 years of age; had not received previous treatment for Chagas disease; *T cruzi* infection was defined as at least 2 reactive serologic tests for patients over 6 months old; or parasitemia in patients less than 6 months of age. Parasitemia was evaluated by the microhematocrit method or polymerase chain reaction for parasite DNA in blood. Serologic tests for Chagas disease were an enzyme-linked immunosorbent assay (Wiener Laboratory, Rosario, Argentina), indirect hemagglutination (Polychaco, Buenos Aires, Argentina), or particle agglutination (Fujirebio, Tokyo, Japan). Subjects who presented with any of the following criteria were excluded from the study: pregnancy; breastfeeding women; treatment with any investigational drug in the month before enrollment; cardiovascular, hepatic, neurologic, endocrine, or other major systemic diseases; and immunocompromised patients.

Patients were treated with 5 to 8 mg/kg benznidazole per day, divided into 2 to 3 daily doses for 60 days (100-mg benznidazole tablets, Radanil; Roche, São Paulo, Brazil).[12] Infants' doses were provided as fractioned tablets and administered with milk. Medication was provided in monthly batches, and compliance was assessed by tablet counting at each visit. Caregivers also were provided with a treatment diary to record doses administered, times of doses, symptoms, and problems associated to the treatment.

A detailed clinical history, physical examination, and laboratory routine tests (hemoglobin, total white blood count, differential white blood cell count, platelets, alanine amino transferase, aspartate amino transferase, total direct and indirect bilirubin, alkaline phosphatase, total cholesterol and creatinine, and pregnancy test in adolescent girls)[1,10] were conducted at diagnosis and at 7, 30, and 60 days after the start of treatment. Eosinophilia was defined as an eosinophil level above 800 μL and abnormal liver enzymes as any value of >32 IU/L for alanine amine transferase and 48 IU/L for aspartate amine transferase.

Signs and symptoms suggesting ADRs were specifically inquired for and recorded during each hospital visit. After the end of the treatment, follow-up took place every 3 months for the first year and every 6 months thereafter. Additional clinical and laboratory evaluations were conducted during any unscheduled visit. Patients were advised to return on any day during the follow-up period if ADRs occurred. All concomitant medications were recorded, and caregivers were told about potential ADRs and provided a telephone number to call in case of doubt or if ADRs appeared.

Clinical safety laboratory evaluations and detection of parasitemia and/or serologic tests for detection of anti-

bodies against *T cruzi* were performed before the start of the treatment with benznidazole and at 7, 30, and 60 days of pharmacotherapy. Cardiologic evaluation, including echocardiogram and electrocardiogram, was conducted before the start of the treatment and 1 year afterward. ADRs were defined according to World Health Organization definitions.[25,26] Causality assessment was performed using World Health Organization criteria[27,28] and the Naranjo score.[29]

The study protocol was approved by the research and teaching committee and bioethics committee of the Children's Hospital "Ricardo Gutierrez" of Buenos Aires and the World Health Organization Secretariat Committee for Research Involving Human Subjects (Geneva, Switzerland). Written consent was required from patients' legal representatives, as well as assent from the patient, as appropriate.

Student's t and χ^2 tests were used to compare continuous and categorical variables, respectively. Continuous variables are presented as means with 95% confidence intervals (CIs) and medians and interquartile ranges (IQRs) and categorical variables as percentages.

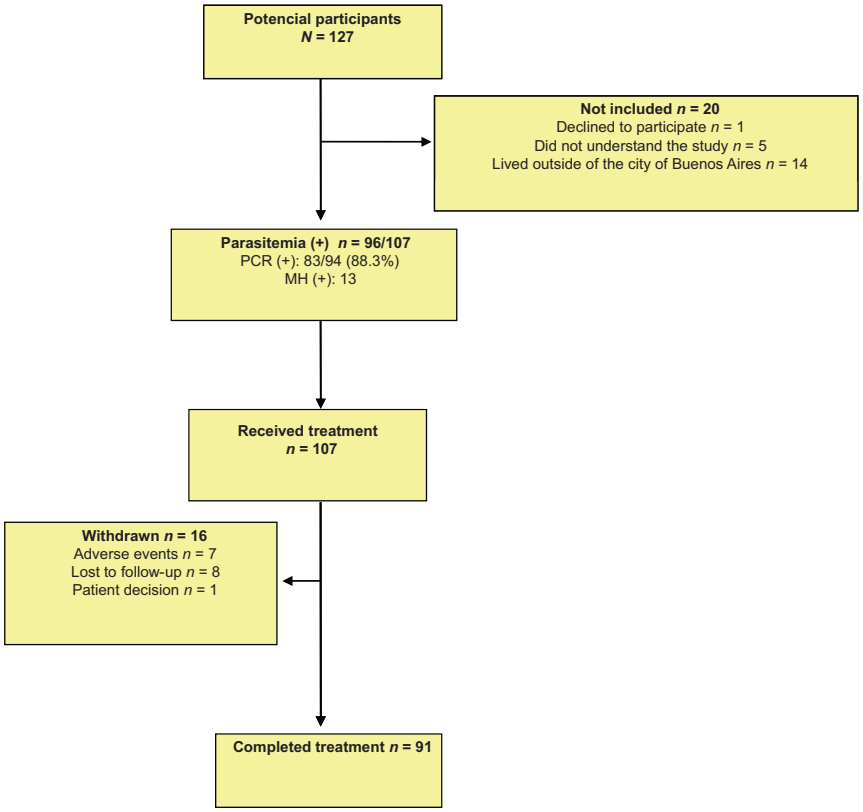

FIGURE 1
Study flowchart.

RESULTS

A total of 107 of 127 eligible patients were enrolled in the study (Fig 1). Participating children mostly were from Buenos Aires. The median age was 6.9 years (range: 10 days to 19 years). Maternal origin of congenitally infected infants was Argentina in 59.8% of cases, Bolivia in 29%, Paraguay in 10.3%, and Brazil in 0.9%. Route of infection was transplacental in 67.3% of patients, vectorial in 4.7%, and undefined in 28%.

All patients were asymptomatic with no cardiac involvement or other Chagas disease–associated pathology at enrollment. Two patients had asthma and 1 patient had epilepsy. Five patients had preexisting laboratory abnormalities, which resolved spontaneously. Four patients had eosinophilias and 1 had mild neutropenia.

The mean benznidazole dose was 6.4 mg/kg per day (range: 5–8 mg/kg per day) in 2 divided doses (76 cases) or in 3 divided doses (31 cases). Mean treatment length was 60 days (95% CI: 59–61). We observed good compliance on the basis of tablet counts and medication registry review. Fifteen subjects received concomitant medications: 5 subjects received β-lactams; 4 steroids (2 budesonide, 2 methylprednisone); 1 vitamins; 1 iron; 1 acetaminophen; 1 valproic acid; 1 carbamazepine; and 2 loratadine. Only 3 patients had ADRs related to benznidazole. All patients recovered uneventfully.

In 107 patients enrolled in the study, we observed 73 adverse events in 55 children. Eleven adverse events, in 11 patients, were considered unrelated to treatment after review of the time course and clinical data, using World Health Organization causality criteria.[27] The remaining 62 ADRs, in 44 patients (41.1% of all patients), were considered to be related to treatment with benznidazole.[27] The most frequent ADRs were dermatologic (22 of 107 subjects [21%]), followed by gastrointestinal (9 of 107 subjects [8.5%]), central nervous system (CNS) (10 of 107 subjects [9%]), and neuromuscular (3 of 107 subjects [2.8%]) events (Table 1). Mean duration of ADRs was 8.2 days (95% CI: 4.1–12). Over two-thirds (44 of 62) of ADRs were clinical, and the remaining 18 were biochemical findings. In 5 patients, we observed both clinical and laboratory ADRs (Table 1). Approximately three-quarters of the patients (32 of 44 [73%]) who had ADRs experi-

TABLE 1 Breakdown of Benznidazole: Related ADRs Observed in This Cohort

	n	%
Total ADRs	62	100
Clinical adverse reactions	44	71
Dermatologic ($n = 22$)		35.5
Rash	10	16.1
Eczema	7	11.3
Pruritus	3	4.8
Polymorphous erythema	1	1.6
Urticaria	1	1.6
CNS ($n = 10$)		16.1
Headache	7	11.3
Blurry vision	2	3.2
dizziness	1	1.6
Gastrointestinal ($n = 9$)		14.5
Vomiting	3	4.8
Abdominal pain	4	6.4
Anorexia	2	3.2
Neuromuscular ($n = 3$)		4.8
Cramps	2	3.2
Myalgia	1	1.6
Biochemical adverse reactions	18	29
Hematologic ($n = 12$)		19.3
Eosinophilia	8	12.9
Leukopenia	4	6.4
Metabolic ($n = 6$)		9.7
Liver enzymes	5	8
Cholesterol	1	1.6

Five patients presented clinical and biochemical adverse events.

TABLE 2 List of Patients Who Abandoned Treatment

Age, y	Reason for Discontinuation	Treatment Day	Comments
19	Rash, moderate; patient decision	9	Good response to symptomatic treatment; lost to follow-up
10	Eczema, moderate; parent decision	29	Good response to symptomatic treatment; lost to follow-up
1	Erythema, polymorphous, moderate; parent decision	7	Good response to symptomatic treatment; lost to follow-up
12	Rash, moderate	7	Good response to symptomatic treatment; lost to follow-up
7	Eczema, severe Medical decision	10	Good response to symptomatic treatment Re-treatment with nifurtimox
18	Rash, severe; patient decision	13	Good response to symptomatic treatment; lost to follow-up
13	Gastrointestinal, adverse events, moderate	14	Good response without treatment; lost to follow-up

enced them in the first 10 days of treatment, with a median time to ADR of 7 days ($IQR_{25–75}$: 3.5–11.0). Effects on the CNS predominated in the first 2 days of treatment (median: 2 days [$IQR_{25–75}$: 2.0–8.5]), followed by gastrointestinal ADRs (median: 5 days [$IQR_{25–75}$: 2.0–8.5]) and dermatologic ADRs (median: 9 days [$IQR_{25–75}$: 7.0–11.0]). Differences between the time of appearance of CNS and dermatological ADRs were statistically significant ($P = .02$; Mann-Whitney test). Mean duration of ADRs was 8.2 days (95% CI: 4.1–12.0 days). Only 3 (7%) ADRs, all mild, were observed in the last 30 days of treatment. No differences were observed in the rate of ADRs between doses or among daily-dose frequencies (ie, 2 vs 3 times daily), and no differences were observed between genders.

The mean age of children with ADRs was 9.9 years (95% CI: 8.2–12) ($n = 44$), which was significantly higher than the age of children without an ADR (mean: 4.8 years [95% CI: 3.7–6.0]; $n = 76$; $P < .001$, *t* test).

The incidence of ADRs was unevenly distributed and directly related to age, being more common in patients over 7 years old (70% of ADRs), which comprised ~50% of the patient population ($P < .001$, χ^2 test). Approximately 36% (38 of 107) of patients within our cohort were children below 2 years of age. Seven of 38 (18%) patients in this subgroup developed ADRs: 3 patients developed rashes; 2 developed eosinophilias; and 2 had increased liver function test values. All patients recovered completely with no complications. One patient, who experienced a generalized rash, was withdrawn from the study by the caregiver's decision. The rate of ADRs was significantly lower in infants and toddlers compared with older children (18% vs 53%; $P < .001$, χ^2 test).

No serious ADRs occurred in our cohort. Fifty (80.6%) ADRs were classified as mild, 10 (16%) as moderate, and 2 (3.2%) as severe. All patients recovered after symptomatic treatment and/or transient discontinuation of benznidazole. The 2 severe ADRs were generalized rash and led to treatment discontinuation. None of the patients had clinical criteria compatible with severe drug reactions, such as drug reaction with eosinophilia and systemic symptoms, Stevens-Johnsons syndrome, or toxic epidermal necrolysis (ie, did not satisfy criteria as outlined by Bastuji-Garin et al[30]). No target lesions, bullae, blisters, or skin necrosis developed, and symptoms resolved quickly with symptomatic treatment and drug discontinuation. Also, no fever was present.

The most common dermatological ADRs were rash and eczema, mostly on limbs and trunk, which lasted a mean of 15 days (95% CI: 7–23 days). Clinical management of dermatologic ADRs was limited mostly to antihistamine medications with good response. Two mild cases with persistent pruritus required symptomatic treatment with loratadine throughout the treatment with benznidazole, but no discontinuation was required (Table 2).

Transient discontinuation of benznidazole because of ADRs was required in 12% (13 of 107) of children (mean duration: 8.9 days [95% CI: 2.6–15.0]). Seven (7 of 13 [54%]) patients temporally discontinued treatment because of ADRs (4 because of rashes, 2 gastrointestinal discomforts, and 1 headache); 2 patients temporarily discontinued treatment because of a momentary lack of medication, 2 other patients because of patient noncompliance, and the last 2 patients because of mild viral ill-

ness. All 13 patients restarted and completed treatment without additional interruptions.

Patients abandoned treatment in 6.5% (7 of 107) cases because of ADRs. Most (6 of 7) patients were over 7 years old (Table 2). One patient was successfully treated with nifurtimox (12 mg/kg per day three times per day for 60 days), and the remaining refused additional treatment. ADRs responsible for treatment interruption were dermatological in 6 cases (2 severe and 4 moderate) and gastrointestinal in 1 case. All patients completely recovered from the ADRs, as confirmed by telephone follow-up. No effects on growth or weight progression were observed in any of the patients.

The most common biochemical ADRs were hematologic, mainly eosinophilia (912–2275 μL) and mild leukopenia (3100–3700 μL) (Table 1). In 2 cases, eosinophilia was associated with mild rash. Hepatic involvement was clear in 5 cases, in which aspartate amino transferase and alanine amino transferase were increased 2 to 10 times but without signs of cholestasis (Table 2). Biochemical ADRs did not require specific measures or treatment interruption, and they resolved completely before the end of the benznidazole treatment.

Treatment response was high and persistent, with over 90% of children who completed 60 days of treatment presenting a steady decrease or disappearance of specific *T cruzi* antibodies and a negative parasitological test (*T cruzi*–specific polymerase chain reaction and a microhematocrit test). All patients were followed after treatment completion for up to 3 years. No long-term adverse consequences of treatment with benznidazole were observed by the treating physicians or reported by parents or patients.

DISCUSSION

We present here one of the largest cohorts published to date of infants and children treated with benznidazole for Chagas disease. Our results confirm clinical observations from previous pediatric cohorts,[7,13,31,32] which have suggested that benznidazole-associated ADRs are mild in children and in most cases do not require treatment interruption.

A previous randomized placebo-controlled study[31] reported a 5% incidence of noncutaneous ADRs in children older than 7 years of age who were treated with benznidazole. These ADRs mainly were anorexia, nausea, headaches, and arthralgias. Maculopapular rash and pruritus also were reported in 12% of patients and linked to treatment interruption in 2% of cases.[31]

Another randomized placebo-controlled study[13] reported a 20% rate of ADRs among children 6 to 12 years old.[13] All reported ADRs were mild or moderate and disappeared with benznidazole discontinuation. Similar to our study, most common ADRs were gastrointestinal and dermatologic.

A large pediatric cohort study[32] of children and adolescents showed that 50.2% of patients from Honduras and 50.8% of patients from Guatemala who were treated with benznidazole had mostly mild (3 severe) ADRs. The most frequent ADRs were gastrointestinal (26.8%), followed by dermatological (13.0%) and neurologic (10.4%). The rate of ADRs in Bolivia was lower (25.6%) in the same study, with increasing risk in patients more than 10 years old. However, 1 case of toxic epidermal necrolysis and 1 of Stevens-Johnsons syndrome were observed (both recovered well).[32] No laboratory abnormalities were reported,[32] but laboratory tests were performed less frequently than in our study.

ADRs have been more commonly reported in adults, and severity seems to be much more significant. Severe ADRs reported in adults include dermatologic reactions, peripheral neuropathy, and leukopenia.[31] None of these severe reactions have been observed in children in significant numbers.

Peripheral neuropathy frequently is observed in adults but is quite uncommon in children,[13,33,34] as confirmed by our study. There is limited clinical data available to suggest a correlation between benznidazole blood levels, or total benznidazole exposure, and ADRs, but peripheral neuropathy seems to be dose dependent to some extent.[34,35] We acknowledge that neuropathy is extremely difficult to rule out in small children. However, after following these children for several years after treatment, no functional deficits or any signs compatible with chronic neuropathy were noted.

The incidence of ADRs in our cohort was strongly associated with the age of the patient, with most ADRs occurring in children over the age of 7 and very few ADRs in infants or toddlers. This suggests that children older than 7 years should be monitored more carefully. This finding confirms previous observations[31,32] and provides reassurance on the safety of benznidazole in younger children, which had not been fully addressed in previous studies. We also observed that neurologic ADRs seemed to occur soon after the start of the treatment, followed by gastrointestinal and then dermatologic ADRs.

Evaluation of CNS ADRs, such as headaches, in infants was difficult because only older children are able to accurately express and describe its symptoms. Nevertheless, associated signs, such as unexplained irritability, food refusal, or vomiting, were not reported by caregivers. Causality evaluation of gastrointestinal ADRs also is problem-

atic because other factors associated with drug administration, such as formulation and tablet size, could be involved in the observed intolerance. The absence of appropriate pediatric formulations complicates matters further, as tablets are not easily (or willingly) swallowed by small children, which sometimes leads to vomiting and other problems that may not be specifically related to the active drug.

Cutaneous ADRs were more likely to occur in the second week of treatment, which was also observed in previous studies.[13,32] Severe reactions such as Stevens-Johnsons syndrome and toxic epidermal necrolysis rarely have been reported, with an estimated incidence of 1 of 3000 subjects,[32] which is similar to that of lamotrigine-induced Stevens-Johnsons syndrome.[36] However, an accurate evaluation of actual benznidazole-associated Stevens-Johnsons syndrome/toxic epidermal necrolysis risks requires improved pharmacovigilance efforts. We also observed a number of laboratory abnormalities, including several cases of eosinophilia and increased liver enzymes. It is interesting to note that patients who initially presented with eosinophilia did not worsen with benznidazole treatment. Asymptomatic increases in liver enzymes generally were mild and did not require treatment modifications. Progress along growth and weight curves were not affected by treatment with benznidazole. This observation is in contrast with the striking anorexia observed in patients treated with the alternative anti–Chagas disease medication, nifurtimox.

Experimental toxicology models suggested an increased risk of lymphoma in rabbits treated with supratherapeutic benznidazole doses.[37] In our cohort, follow-up after 3 years did not show any evidence of increased risk for malignancies. It is reassuring that an increased risk for any cancers has never been observed in adult or pediatric cohorts to date.[12,23,32,38] Viotti et al[23] reviewed their experience with 1047 patients treated with benznidazole and found no increased risk for cancer (mean follow-up: 7.5 years); this also is in agreement with the experience at our institution, with more than 500 pediatric patients treated with benznidazole and prolonged follow-up.

The pharmacologic basis for the marked difference in incidence and severity of ADRs reported between children and adults remains to be clarified. However, examples abound of medications metabolized at different rates in children and adults, in some cases leading to differential toxicity. Notably, children 2 to 6 years of age seem to have faster elimination rates than adults for many drugs.[39–41] This faster elimination rate, combined with scarce data, suggests that hepatic elimination of benznidazole provides a plausible explanation for differences in ADRs incidence among children and adults.

Unfortunately, there have been no reported studies to date that evaluated the pharmacokinetics of benznidazole in children. Preliminary results from a population pharmacokinetics study in our institution (www.clinicaltrials.gov identifier NCT00699387) suggest that plasma concentrations are, indeed, significantly lower than those reported in adults, but these results require confirmation.[42]

CONCLUSIONS

Our results support previous observations[13,31,43] that benznidazole-associated ADRs in children generally are mild. Infants and toddlers seem to be at very low risk for severe ADRs and are likely to respond well to the medication. There seem to be few reasons, at this point, to deny effective treatment to children on the basis of theoretical risks not confirmed by any studies performed to date. However, treatment for infants and children with Chagas disease still is commonly postponed to protect them from ADRs, which leads to progression of the disease, reduces the chances for cure, and potentially exposes children to a higher risk for the severe ADRs that have been observed in older patients but virtually absent in children younger than 7 years.

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