

Allergy to benznidazole: cross-reactivity with other nitroimidazoles

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Clinical Implications

- Based on a case series of 6 patients, patch testing appears to be useful in confirming delayed hypersensitivity to benznidazole and determining cross-reactivity with metronidazole.

TO THE EDITOR:

Benznidazole (Bzn) is a nitroimidazole drug used as first-line treatment for Chagas disease (CD), a potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi*, which is vectored by triatomine insects.¹

Migration of the population in recent years has allowed the infection to spread from South America, where it is endemic, to other continents where the infection was not previously found, such as North America or Europe. Treatment for CD remains a challenge because the only drug that has shown efficacy is Bzn, a nitroheterocyclic compound that can be given alone or in combination with other drugs.²

Several side effects had been reported with Bzn: anorexia, nausea, vomiting, headache, psychological disorders and polyneuropathies, and skin reactions. Although skin reactions are most frequent,² confirmed allergy to Bzn is rare, and there are only a few cases reported in the literature.³⁻⁶

Only nonimmediate type IV hypersensitivity reactions have been described, mostly generalized exanthems, but also localized dermatitis, acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms, and even toxic epidermal necrolysis.^{3,4} It is important to correctly diagnose Bzn allergy and identify cross-reactivity with other nitroimidazole drugs to provide management advice regarding future nitroimidazole use. This is especially important in these types of patients, who frequently suffer from other parasitic infections that are endemic in their region.

Metronidazole (Mtn) belongs to nitroimidazole drugs, and, although it is not effective for treating CD, it is useful for other infectious diseases caused by protozoan parasites and anaerobic bacteria. Therefore, we think that it is essential to include Mtn in the allergy evaluation to give patients an alternative drug from the nitroimidazole group that is often needed.

We report a series of 6 patients referred to our allergy department with suspected hypersensitivity reactions to Bzn. The aim of this study was to establish the utility of a patch test (PT) to confirm the diagnosis and to identify cross-reactivity between Bzn and Mtn.

Six patients diagnosed with CD by the Infectious Disease Service of our hospital were treated with Bzn. All of them were women, with a median age of 33 years (range, 27-43 years), who were born in Bolivia (South America) and had been living in Spain for more than 10 years.

After several a median of 7.5 days of treatment (range, 3-15 days), all presented an itchy maculopapular generalized exanthem that resolved with antihistamines and corticosteroids in 15-20 days. Three patients developed desquamation and residual lesions. None of these patients had histories of adverse reactions to Mtn.

All patients underwent PT with Bzn and Mtn 10% in dimethylsulfoxide (Nonwoven Patch test Strips Curatest; Lohman&Rauscher International, Rangsdorf, Germany) (Table 1).

Readings were taken at day 2 (D2) and day 4 (D4). Of the 6 patients, 5 had positive PT to Bzn at D2 and D4 (Figure 1).

Patient 1, with negative PT with Bzn, underwent a single blind oral challenge test (SBOCT) to rule out allergy to this drug. Two hours after the intake of 100 mg of Bzn, the patient developed a maculopapular generalized exanthem and a flare-up phenomenon in the Bzn PT. The reaction resolved with antihistamines and corticosteroids in 3 days.

PT with Mtn was negative in 4 patients (Figure 1). In patients 4 and 5, PT was positive at D2 and D4. PT with Mtn and Bzn were both negative in 6 healthy controls.

SBOCT with Mtn was negative in 3 patients with negative PT. One patient refused a SBOCT with Mtn.

Thus, PT with Bzn was diagnostic in 5 of 6 patients (83.3%), and in 1 case, even though PT was negative, a positive SBOCT and flare-up of PT confirmed allergy to Bzn. PT with Bzn presumably has a high sensitivity because nearly all of the patients could be diagnosed by PT. It is not possible to determine the specificity of the PT in these patients because we did not consider it ethical to perform a SBOCT with the culprit drug in light of a compatible clinical history and a positive PT.

We conclude that PT to Bzn was very useful for the diagnosis in our series of patients, suggesting a nonimmediate type IV hypersensitivity mechanism. These findings are of significance because in severe delayed skin reactions^{3,4} SBOCT is contraindicated and PT can help clinicians to confirm the diagnosis without substantial risks.

Cross-reactivity between Bzn and Mtn was found in 2 of 6 patients (33.3%) in our series who were sensitized to both nitroimidazole drugs.

Three of three of patients with negative PT to Mtn had negative SBOCT, leading to a negative predictive value of 100% in this small series.

To our knowledge, there are no cases published in the literature of cross-reactivity between these 2 nitroimidazole drugs. There are some cases reported of allergy to Mtn and to other imidazoles with cross-reactivity between them, but none of them reported these data with Bzn and Mtn.^{7,8}

Our experience highlights the importance of testing to both Bzn and Mtn in patients with reactions to either drug, because cross-reactivity exists but is not consistent.

TABLE I. Allergy study

Patients	PT		SBOCT	
	Bzn	Mtn	Bzn	Mtn
1	—	+	+	NP
2	+	—	NP	—
3	+	—	NP	—
4	+	+	NP	NP
5	+	+	NP	NP
6	+	—	NP	—

Bzn, Benznidazole; Mtn, metronidazole; NP, not performed; PT, patch test; SBOCT, single blind oral challenge test.

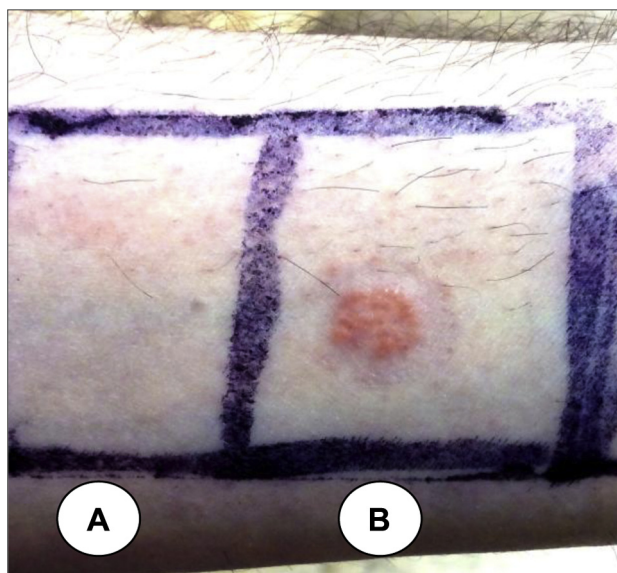


FIGURE 1. Patient number 3. A, Negative PT with Mtn. B, Positive PT with Bzn. Bzn, Benznidazole; Mtn, metronidazole; PT, patch test.

Álava-Cruz et al³ reported a case report of AGEP due to Bzn, which had a positive PT with a skin biopsy of the lesion that confirmed the diagnosis. Also this patient had negative PT to Mtn, but no SBOCT could be performed to confirm tolerance because of refusal from the patient.

González-Ramos et al⁴ reported a case of overlap-severe cutaneous adverse reaction to Bzn, confirmed by biopsy and positive lymphocyte transformation test. No PT were performed in these cases.

As far as we know, there are no case reports published in the literature showing that PT to Bzn can safely identify a high proportion of patients with likely Bzn allergy.

We also present the novel observation that cross-reactivity with Mtn is not infrequent but is not invariable in patients with Bzn allergy. In our series, 33.3% of patients had positive patch tests to both drugs, emphasizing the value of testing to both drugs in patients with histories of adverse reactions to either.

Because our report does describe only 6 patients, more studies and more patients are needed to confirm these findings.

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