

A case of systemic contact dermatitis secondary to edetate disodium

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Clinical Implications

- We report a case of systemic contact dermatitis due to edetate disodium.
- Systemic contact dermatitis can be provoked by cutaneous administration despite not causing a positive patch test result.
- Patch testing might be useful in the future with single antigens to try to provoke an attack and identify a specific antigen.

TO THE EDITOR:

Baboon syndrome was first described in 1984 in 3 cases of systemic allergic contact dermatitis secondary to topical sensitization with ampicillin, nickel, and mercury.¹ The patients presented with a diffuse symmetrical erythema, predominantly on major flexural areas, and inverted triangular or V-shaped erythema on both upper anteromedial thighs. In more recent years, a distinction has been made between topical drug-induced and systemic drug-induced baboon syndrome.² Several agents have been previously implicated including nickel, heparin, pseudoephedrine, terbinafine, and several antibiotics.³ The acronym SDRIFE (symmetrical drug-related intertriginous and flexural exanthema) was proposed in 2004 to describe cases related to systemic drugs without previous sensitization.⁴ Most recently, subclassifications of baboon syndrome were created including contact allergen-induced baboon syndrome (excludes drugs), topical drug-induced baboon syndrome, and systemic drug-induced baboon syndrome, all of which occur with previous cutaneous sensitization.⁵ SDRIFE is a separate classification that refers to cases that occur without previous cutaneous sensitization and in which patients develop typical erythema of the gluteal/inguinal area on systemic exposure to a drug.

Here, we report the case of a 76-year-old man referred for an episodic erythematous eruption occurring primarily over the buttocks for 9 months and lasting 1 week before desquamating. With each episode he felt a prodrome of malaise and fatigue the evening before rash onset. He recalled that nearly every time the eruption occurred it was within 48 hours of his use of azelastine and once with ipratropium nasal spray. He also recalled that on at least 3 occasions he had drunk Merlot wine the evening before but otherwise rarely drank alcohol. He had no history of allergic contact dermatitis or drug eruption. During an eruption, physical examination revealed a healthy-appearing man with a normal head and neck examination, clear lungs, and demarcated area of marked erythema over the buttocks (Figure 1). Shave biopsy demonstrated a neutrophilic exocytosis with interstitial neutrophilic dermatosis with eosinophils. Patch testing was performed to the North American contact dermatitis 65 series as well as

Merlot wine, ethanol, isopropyl alcohol, azelastine nasal spray, ipratropium nasal spray, and pure azelastine (0.1% to 10%) in both petrolatum and aqueous solutions. These were completely negative at both 48 and 96 hours when applied in duplicate to his upper back and buttocks.

He subsequently experienced 2 further outbreaks, both within 48 hours of using the commercial generic azelastine nasal spray. He also challenged himself with ipratropium nasal spray with and without Merlot wine without any reaction. Azelastine powder was used to make a 0.2% nasal spray without any preservatives. Repeated use of this led to no outbreak of symptoms.

After another reaction to commercial azelastine nasal spray, a workup for hypersensitivity to an additive was undertaken. Patch testing was performed to benzalkonium chloride 0.1%, edetate disodium 1%, hydroxypropyl methylcellulose 5%, citric acid 1%, and dibasic sodium phosphate 1% over both back and buttocks, which were negative at 48 and 120 hours, but the patient had a typical outbreak and rash 8 days later. Patch testing was then performed individually to each of the additives in separate weeks. Within 12 hours of the placement of the patch with edetate disodium 1%, the patient had typical prodromal symptoms and a reaction over the right buttock and the right thigh.

We concluded that edetate disodium was the inciting agent for the patient's rash. Since identifying and avoiding this antigen he has had 2 further episodes related to a sunscreen and shampoo that contained edetate disodium. Patch testing confirmed sensitization to edetate disodium with a reproducible systemic contact dermatitis outbreak despite the absence of a typical positive localized patch test result.

Ethylenediaminetetracetic acid (EDTA) and its salt (edetate disodium) have been widely used as preservatives, antioxidants, and metal chelators in multiple medications including topical therapy for the eye and nose as well as cosmetics.⁶ EDTA was first reported to cause contact dermatitis in 1969 by Raymond and Gross in a patient after topical application of a steroid cream.⁷ Although ethylenediamine has been implicated as the provoking factor for systemic contact dermatitis in 2 previous reports,^{8,9} it is chemically and antigenically distinct from EDTA.¹⁰

It is noteworthy that our patient's reaction occurred secondary to a nasal spray rather than a systemically administered drug. It is also interesting that the eruption was reportedly more severe after drinking wine while using the azelastine with edetate disodium. We hypothesize that intranasal vasodilation as a consequence of alcohol ingestion may lead to increased absorption and hasten the reaction because there was a delay when red wine was not ingested. There have been reports of topical drug-induced systemic contact dermatitis secondary to antibiotics and local anesthetics. However, to our knowledge, this is the first reported case of systemic contact dermatitis, specifically baboon syndrome, occurring with edetate disodium administered in a nasal spray.

We highlight 2 important issues that this case brings up. First, systemic contact dermatitis or baboon syndrome can occur after the administration of the antigen nasally. It is likely that at high enough concentrations, enough systemic absorption takes place to trigger systemic symptoms. Second, although a typical



FIGURE 1. Patient's skin rash at the time of reaction.

T-cell-mediated delayed hypersensitivity-type reaction is suspected, we were unable to demonstrate a positive patch test result. Despite a negative patch test result, we were able to provoke the entire systemic syndrome by sequentially applying individual patch tests to each inactive ingredient. Although this method of diagnosis is cumbersome, in a motivated patient it can

be useful to identify a specific causative agent if conventional patch testing result is negative.

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Conflicts of interest: J. P. Rajan is employed by Scripps Clinic. A. A. White is employed by Scripps Clinic and has received research support from Scripps Clinic Medical Group (Research and Education grant). R. Cornell declares no relevant conflicts.

Received for publication June 25, 2014; revised December 30, 2014; accepted for publication January 26, 2015.

Available online April 22, 2015.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.01.025>

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