

CONTACT POINT

Cutaneous adverse drug reaction after apomorphine infusion, possibly caused by a systemic type IV hypersensitivity reaction to sodium metabisulfite: Report of 2 cases

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CASE REPORTS

Case 1. A 66-year-old man with a 6-year history of Parkinson's disease, and no history of allergy or atopic diseases, was treated with L-dopa, rotigotine, paroxetine and domperidone for several months. Because of severe motor response fluctuations and dyskinesia, he started with continuous subcutaneous apomorphine infusion during waking hours. Apomorphine was started at a dose of 1 mg/h, and gradually increased to 5 mg/h at hospital discharge on day 10. On day 11, the patient developed a maculopapular exanthema on his trunk and extremities (Figure 1). On day 13, a skin biopsy of the rash on his right upper leg showed perivascular, lymphocytic dermatitis with some eosinophils, compatible with a cutaneous adverse drug reaction. Apomorphine was continued and the rash was left untreated; it resolved spontaneously 1 week after presentation.

Case 2. A 44-year-old, non-atopic woman with a 5-year history of Parkinson's disease, hypothyroidism and iron deficiency was treated for more than 1 year with L-dopa, ropinirole, entacapone, levodopa, omeprazole, ferrous fumarate, l-nestrenol, and vitamin C. She started with continuous subcutaneous apomorphine infusion during waking hours for the treatment of motor response fluctuations and dyskinesia. Two days prior to initiation of apomorphine, she was treated with domperidone to avoid peripheral side-effects of apomorphine. On day 14, she developed erythema on her trunk, together with a feeling of being hot, nausea, and a tendency to collapse. Her blood pressure was 120/70 mmHg. Apomorphine treatment was stopped, and the erythema disappeared after a couple of days. No skin biopsy was performed.

Patch testing was performed with our extended European baseline series, a cosmetic series, and a fragrance series. Apomorphine hydrochloride solution for infusion (Britannia Pharmaceuticals,

Reading, UK), which contains apomorphine (0.5%), sodium metabisulfite (0.05%), and hydrochloric acid, was patch tested "as is" and in serial dilutions (50% and 10% aq.); sodium metabisulfite 1.0% pet. was also tested. Subsequently, the substance apomorphine hydrochloride hemihydrate (Spruyt Hillen, IJsselstein, The Netherlands) was patch tested at 1%, 3%, 10% and 30% pet. and aq. The extended European baseline series was tested by combining panels 1 and 2 of the TRUE Test and using an investigator-loaded system (Smartpractice, Barsbüttel, Germany). Van der Bend chambers (Van der Bend, Brielle, The Netherlands) and Fixomull stretch (BSN Medical, Hamburg, Germany) were used to occlude the allergens for 2 days on the back. Reactions were read on day (D) 3 and D7, according to ESCD guidelines.¹ Patch testing showed + positive patch test reactions to sodium metabisulfite on D3 and D7 in both cases (Table 1). Case 2 also had + reactions to apomorphine solution "as is" on D3 and D7 (Figure 2). Patch testing with the substance apomorphine hydrochloride hemihydrate gave negative results in both cases.

Prick tests were performed on the volar aspect of the forearm with apomorphine hydrochloride solution "as is" and in serial dilutions (50% and 10% aq.). Histamine served as a positive control, and saline served as a negative control. The results of the prick tests were negative after 20 minutes and on D3 in both cases. In case 2, the negative prick test results after 20 minutes were followed by intradermal tests with the same substances. These tests gave negative results after 20 minutes and on D3.

DISCUSSION

Hypersensitivity reactions to sodium metabisulfite are well known. Sodium metabisulfite contact allergy was seen in 3.12% of

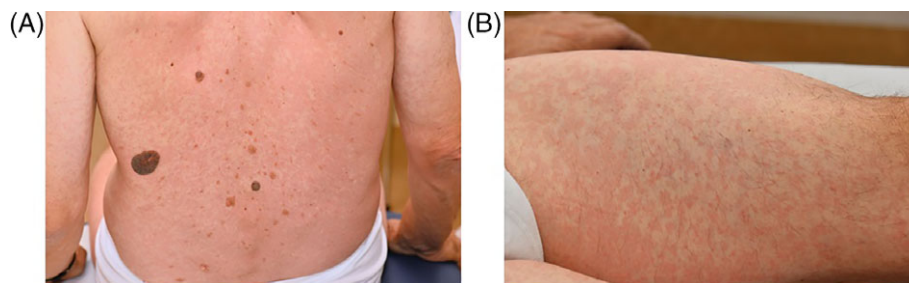


FIGURE 1 Maculopapular exanthema of case 1. (A), Maculopapular exanthema on the back. (B), Maculopapular exanthema on the legs

TABLE 1 Overview of patch test results

Test substance ^a	Concentration	Day 3		Day 7	
		Case 1	Case 2	Case 1	Case 2
Sodium metabisulfite	1% pet.	+	+	+	+
Apomorphine hydrochloride solution 0.5%	"as is"	-	+	-	+
Apomorphine hydrochloride solution 0.5%	10% and 50% aq.	-	-	-	-
Apomorphine hydrochloride hemihydrate	1%, 3%, 10% and 30% aq.	-	-	-	-
Apomorphine hydrochloride hemihydrate	1%, 3%, 10% and 30% pet.	-	-	-	-

^a Only relevant patch test results are shown. Case 1 also had a + positive reaction to limonene hydroxyperoxide on day (D) 3. Case 2 had + positive reactions to nickel sulfate and Amerchol L101 on D3 and D7. These were not considered to be clinically relevant.



FIGURE 2 Patch test results of case 2. Positive reactions to sodium metabisulfite and apomorphine hydrochloride solution 0.5% "as is" including sodium metabisulfite

consecutively patch tested dermatitis patients.² Reports of contact dermatitis after topical application of sodium metabisulfite or after occupational exposure are numerous.³ Moreover, systemic reactions after exposure to sodium metabisulfite have been reported: of 2763 patients, 124 (4.5%) showed positive patch test reactions to sodium metabisulfite, and 6 of these had systemic symptoms, including malaise, nausea, and dizziness ($n = 4$); 1 each had asthma and urticarial lesions.⁴ After consuming a high-sulfite diet, a man presented with a non-pruritic rash on his axillae and groins.⁵ A positive patch test reaction to sodium metabisulfite suggested systemic type IV allergy.

Allergic contact dermatitis caused by apomorphine has been reported in a caregiver and in three occupational pharmacy workers.⁶⁻⁸ All cases showed positive patch test reactions to apomorphine solution; sodium metabisulfite was not tested. No systemic type IV reaction to apomorphine (including sodium metabisulfite) has been

described in the literature. In a recent retrospective analysis on the use of apomorphine in 230 patients, rash was reported 8 times without further specification.⁹ Pot et al reported a case with maculopapular exanthema on the trunk after 16 days of apomorphine treatment.¹⁰ Prick tests with apomorphine solution gave negative results; patch tests with apomorphine and sodium metabisulfite were not performed.

We describe 2 cases with cutaneous adverse drug reactions after 2 weeks of apomorphine treatment, presumably caused by a systemic type IV hypersensitivity reaction to sodium metabisulfite. Because of the severe reaction, case 2 had to stop apomorphine treatment, whereas, in case 1, apomorphine was continued and the rash resolved within a couple of weeks. A low dose of sodium metabisulfite might have caused hyposensitization, which has been shown in systemic nickel allergy syndrome¹¹ and delayed drug hypersensitivity reactions,¹² although the mechanism of hyposensitization is not understood. The negative patch test result with apomorphine solution in case 1 can probably be explained by a dose of sodium metabisulfite lower than the threshold for elicitation when it is patch tested.

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