Introduction

Sodium metabisulfite (CAS no. 7681-57-4; synonyms sodium disulfite, sodium pyrosulfite) is ubiquitous present in cosmetics, pharmaceutics, food and beverages. It is added to products to inhibit oxidation of an active compound in oral, topical and parenteral medication, including apomorphine (CAS no. 314-19-2; synonym apomorphine hydrochloride). Apomorphine is a mixed D1 and D2 dopamine receptor agonist, used as subcutaneous injection or as continuous subcutaneous infusion in the treatment of advanced Parkinson's disease. We present two cases with an adverse drug eruption after treatment with apomorphine infusion, possibly caused by systemic type IV hypersensitivity reaction to sodium metabisulfite, an antioxidant in the apomorphine solution.

Case reports

Case 1 is a 66-year-old man with a 6-year history of Parkinson's disease, and no history of allergy or atopic diseases. He was treated with L-dopa, rotigotine, paroxetine and domperidone for several months. Due to severe motor response fluctuations and dyskinesia he started with continuous subcutaneous apomorphine infusion during waking day (hours patient is awake). Apomorphine was started in a dosage of 1 mg/hr and gradually increased to 5 mg/hr at hospital discharge at day 10. At day 11, he developed a maculopapular exanthema on his trunk and extremities (Figure 5.1). At day 13, a skin biopsy of the rash at his right upper leg revealed a perivascular, lymphocytic dermatitis with some eosinophils, which is compliant with an adverse cutaneous drug eruption. Apomorphine was continued and the rash was left untreated which resolved spontaneously a week after presentation.

Case 2 is a 44-year-old, non-atopic woman with a 5-year history of Parkinson's disease, hypothyroidism and iron deficiency, who was treated for more than a year with L-dopa, ropinirole, entacapone, levothyroxine, omeprazole, ferrous fumarate, lynestrenol and

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**FIGURE 5.1** Maculopapular exanthema of case 1. (A) Maculopapular exanthema on the back. (B) Maculopapular exanthema on the legs.
Chapter 5

vitamin C. She started with continuous subcutaneous apomorphine infusion during waking day for 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. At day 14, she developed an erythema on her trunk, together with a feeling of fever, 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 had been performed.

Patch testing was performed with our extended European baseline series, cosmetic series and fragrance series. Apomorphine hydrochloride solution for infusion (Britannia Pharmaceuticals, Reading, United Kingdom) which contains apomorphine (0.5%), sodium metabisulfite (0.05%) and hydrochloric acid) was patch tested ‘as is’ and in serial dilutions (50% and 10% in aq.) and sodium metabisulfite 1.0% pet was tested. Subsequently, the substance apomorphine hydrochloride hemihydrate (Spruyt Hillen, IJsselstein, the Netherlands) was patch tested in 1%, 3%, 10% and 30% pet. and aqua.

The extended European baseline series was tested with panel 1 and 2 of the TRUE™ test and investigator loaded system (Smartpractice, 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 at day (D) 3 and D7, according to European Society of Contact Dermatitis (ESCD) guidelines.1

Patch testing showed a 1+ positive patch test reaction to sodium metabisulfite at D3 and D7 in both cases (Table 5.1). Case 2 also reacted 1+ positively to apomorphine solution ‘as is’ at D3 and D7 (Figure 5.2). Patch testing with the substance apomorphine hydrochloride hemihydrate remained negative in both cases.

Skin 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, while saline served as negative control. Results of the skin prick tests were negative after 20 min and at D3 in both cases. In case 2, the negative skin prick tests at 20 min. were followed by intradermal tests with the same substances. These tests remained negative at 20 min. and at D3.

**Discussion**

Although its ubiquitous use, hypersensitivity reactions sodium metabisulfite are well known. The prevalence of sodium metabisulfite contact allergy based on patch testing in consecutive dermatitis patients showed a prevalence of 3.12%.2 Reports of contact dermatitis after topical application of sodium metabisulfite or after occupational exposure are numerous.3 Also systemic reactions after exposure to sodium metabisulfite
### TABLE 5.1 | Overview of patch test results.

<table>
<thead>
<tr>
<th>Test substance*</th>
<th>Concentration</th>
<th>D3</th>
<th>Case 1</th>
<th>Case 2</th>
<th>D7</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium metabisulfite</td>
<td>1% pet.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Apomorphine hydrochloride solution 0.5%</td>
<td>'as is'</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Apomorphine hydrochloride solution 0.5%</td>
<td>10% and 50 aq.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Apomorphine hydrochloride hemihydrate</td>
<td>1%, 3%, 10% and 30% aq.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Apomorphine hydrochloride hemihydrate</td>
<td>1%, 3%, 10% and 30% pet.</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*only relevant patch tests results are shown. Case 1 also reacted 1+ positively to limonene hydroxyperoxide at D3. Case 2 reacted 1+ positively to nickel sulfate and amerchol L101 at D3 and D7. These were not considered clinically relevant.

**FIGURE 5.2 | Patch test results of case 2. Positive reactions to sodium metabisulfite and apomorphine hydrochloride solution 0.5% "as is" including sodium metabisulfite.**
have been reported. In a large series of 2763 patients, 124 (4.5%) patch tested positively to sodium metabisulfite, of which 6 patients had systemic symptoms, including malaise, nausea and dizziness (n = 4), asthma (n = 1) and 1 had urticarial lesions. After a high-sulfite diet, a man presented with a non-pruritic rash on his axillae and groins. A positive patch test to sodium metabisulfite suggested a systemic type IV allergy.

Allergic contact dermatitis to apomorphine has been reported in a caregiver and in 3 occupational pharmacy workers with apomorphine. All cases showed positive patch test reactions to apomorphine solution, while 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. Pot et al. reported a case with a maculopapular exanthema on the trunk after 16 days of apomorphine treatment. Skin prick tests with apomorphine solution remained negative while patch tests with apomorphine and sodium metabisulfite were not performed.

We describe 2 cases with a cutaneous adverse drug reaction after 2 weeks of apomorphine treatment, presumably caused by a systemic type IV hypersensitivity reaction to sodium metabisulfite. Due to the severe reaction, case 2 had to stop apomorphine treatment, whereas in case 1 apomorphine was continued while 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 syndrome and delayed drug hypersensitivity reactions, though the mechanism of hyposensitization is not understood. The negative patch test reaction to apomorphine solution in case 1 can probably be explained by a dose of sodium metabisulfite lower than the threshold for elicitation.
References
