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(Citation)
Allergology International,70(3):398-400

(Issue Date)
2021-07

(Resource Type)
journal article

(Version)
Version of Record



(URL)
https://hdl.handle.net/20.500.14094/90008869

Allergology International 70 (2021) 398–400

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

# Skin tests and immunohistochemical analyses of erythroderma caused by sodium bisulfite

*Dear Editor,*

Although sulfites act as antioxidants and are widely used as preservatives in many drugs, foods, and cosmetics, they can invoke adverse responses, such as bronchial asthma-like symptoms, anaphylactic shock, and erythema.[1–5] Some patients show adverse responses via allergic reactions, and others show them via mechanical stimulation.[1–4] Despite the awareness regarding sulfite-related adverse effects, no specific diagnostics tests and classification guidelines exist for these reactions.[1–3,5,6] Moreover, there are several forms of sulfites, such as sodium bisulfite ($NaHSO_3$), sodium metabisulfite ($Na_2S_2O_5$), and sodium sulfite ($Na_2SO_3$) (Fig. 1A–C).[6] Whether these sulfites may react similarly remains unclear.[6] To the best of our knowledge, we present the first case with erythroderma caused by an intravenous injection containing sodium bisulfite. Additionally, we investigated the suitability of tests to diagnose adverse responses to sulfites and potential cross-reactivity between sulfites.

Our patient was a 71-year-old woman with no history of allergies. She received an intravenous injection containing a mixture of chondroitin sulfate sodium and sodium salicylate (Kashilon®), and an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus (Neurotropin®) to treat cold symptoms. The next morning, erythema with pruritus occurred all over her body (Fig. 1D, E). Neither pustules, plaques, nor clear lymphadenopathies were found. Blood test results were normal, including autoantibodies, except for the increased blood eosinophil count (693/μl). We ruled out infection-associated eruptions, acute generalized exanthematous pustulosis, psoriasis, parapsoriasis, and Ohfuji's disease, which can also present erythroderma. Histopathological examination showed liquefaction degeneration in the basal layer of the epidermis; eosinophils surrounded the blood vessels of the dermis (Fig. 1F). Immunohistochemical analyses revealed infiltration of CD3-positive lymphocytes consisting of CD4-positive and CD8-positive lymphocytes in superficial dermis (Fig. 1G–I). Oral antihistamine and steroid ointment were ineffective. However, systemic prednisolone (20 mg/day) cured the eruption.

After obtaining written informed consent, we tested the patients to identify the cause of erythroderma. For Neurotropin®, the patch test (as is), intracutaneous test (diluted 10-fold), and intravenous injection were negative. For Kashilon®, the patch test (as is) (Table 1) was positive (as defined by the recommendations of the International Contact Dermatitis Research Group). Intracutaneous hypersensitivity test using a Kashilon® (diluted 10-fold and 100-fold) was positive. Therefore, the components of Kashilon® were examined. Patch tests with sodium salicylate and sodium chondroitin were negative. Oral provocation using each drug in the chondroitin sulfate sodium–sodium salicylate mixture (sodium salicylate, 200 mg; sodium chondroitin, 400 mg) was also negative.

Therefore, we suspected sodium bisulfite (a preservative in Kashilon®) as the potential inducer. The 1% sodium bisulfite patch test prepared in physiological saline[1] was positive (Table 1). Interestingly, however, oral provocation at a high dose (200 mg) was negative. The 0.1% of sodium bisulfite patch (Table 1), the skin prick, and intracutaneous tests (0.05%, 0.005%) were also negative.

We also studied other sulfites. While 1% sodium metabisulfite patch test was positive (Table 1), the oral provocation test (200 mg) was negative. For sodium sulfite, the patch (Table 1), intradermal (0.05%, 0.005%), and oral provocation tests (200 mg) were negative. Kashilon® formulation only contained sodium bisulfite. We, therefore, confirmed the diagnosis erythroderma caused by sodium bisulfite.

Prenner and Stevens first reported adverse reaction to sodium bisulfite used in foods and concluded that specific IgE antibody to sodium bisulfite caused the reaction.[7] Some reports mentioned of bisulfite-induced asthmatic reactions caused by mouthwash that generated $SO_2$ within the oral cavity and pharynx.[2,5] While the patients tested positive for some sulfite tests, other tests were negative.[3] Giffon expressed a possibility of sulfite sensitivity caused by the combination of sulfites in foods[3]; however, oral provocation test using a combination of all materials showed a negative result in our study.

Sulfites may elicit adverse reactions via multiple mechanisms, manifesting as immediate (type I) IgE-mediated hypersensitivity reactions, delayed-type (type IV) hypersensitivity reaction, or reflex bronchoconstriction caused by sulfur dioxide ($SO_2$) gas.[1,2,5–8] The 1% patch test was found suitable for drug eruptions caused by delayed-type hypersensitivity, prick or intracutaneous tests for immediate hypersensitivity, and inhalation tests that generate $SO_2$ for the mechanical stimulus-response to $SO_2$ related to asthma.[1,2,5–8] Our findings were consistent with previous reports[1]; the 1% patch test is suitable for delayed-type hypersensitivity. Notably, 1% patch test of sodium bisulfite on a healthy control showed the negative result.

Skin prick test, intracutaneous test, oral provocation test, or reflex bronchoconstriction caused by $SO_2$ gas could not confirm adverse reaction in our patient. We conjectured that same sulfite might elicit different types of hypersensitivity reactions in a patient

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2021.01.003

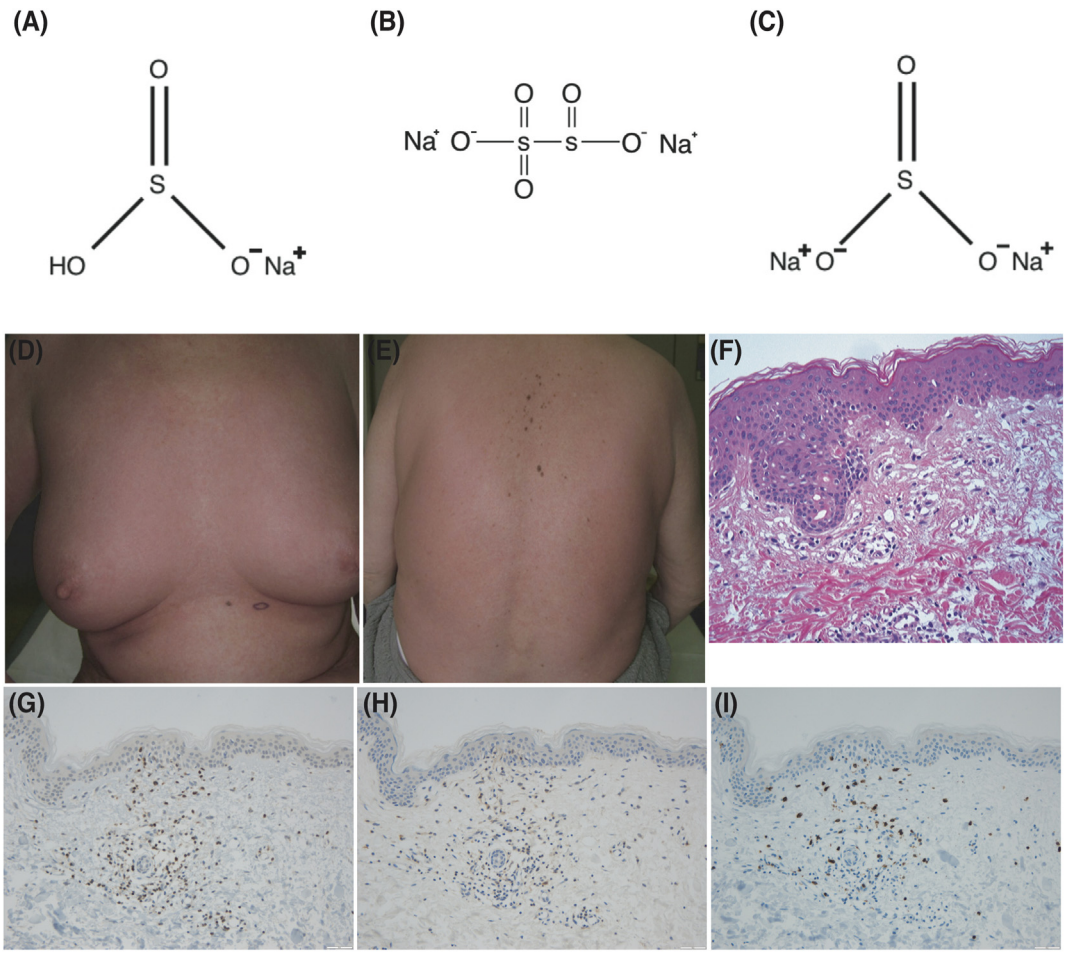


**Fig. 1.** **(A–C)** Structural formulae of sodium bisulfite ($NaHSO_3$) **(A)**, sodium metabisulfite ($Na_2S_2O_5$) **(B)**, and sodium sulfite ($Na_2SO_3$) **(C)**. **(D, E)** Erythema with pruritus all over her body. **(F)** Histopathological examination of a specimen of the erythematous lesion from breast tissue revealing liquefaction degeneration in the basal layer of the epidermis; lymphocytic infiltration and eosinophils around the blood vessels of the dermis are also observed (H&E staining, original magnification, 200×). **(G)** Lymphocytes in the superficial dermis are positive to immuno-staining with CD3 (original magnification, 100×). **(H)** Lymphocytes in the superficial dermis are positive to immuno-staining with CD4 (original magnification, 100×). **(I)** Lymphocytes in the superficial dermis are positive to immuno-staining with CD8 (original magnification, 100×).

**Table 1**
The reactions of patch tests.

| | % | 48 h | 72 h | 7 days |
|---|---|---|---|---|
| Mixture of chondroitin sulfate sodium and sodium salicylate | as is | + | + | + |
| Sodium salicylate | 0.1% | − | − | − |
| | 1% | − | − | − |
| | 10% | − | − | − |
| Sodium chondroitin | 0.1% | − | − | − |
| | 1% | − | − | − |
| | 10% | − | − | − |
| Sodium bisulfite | 1% | + | + | + |
| | 0.1% | − | − | − |
| Sodium metabisulfite | 1% | + | + | − |
| Sodium sulfite | 1% | − | − | − |

via immediate (type I) IgE-mediated hypersensitivity reaction or drug eruptions and contact dermatitis caused by delayed-type (type IV) hypersensitivity. Sodium bisulfite is an antioxidant and might be easily digestible due to chemical instability. However, this hypothesis should be tested in future studies. Skin tests in our patient showed erythroderma caused by sodium bisulfite via delayed-type hypersensitivity.

One report has described that cross-reactivity between sulfites is very low since sulfite can be formed under appropriate conditions only.[1] Another report has described that the majority of patients showing a positive reaction to sodium metabisulfite are also positive to sodium sulfite.[6] Interestingly, our case showed cross-reactivity between sodium bisulfite and sodium metabisulfite. Cross-reactivity might depend on the types of adverse responses to sulfites.

Vitamin B12, atropine, and sodium cromoglycate could prevent bronchospasm caused by sulfites, however, this is not effective with other types of reactions.[3] Aggregating reports of rare cases is essential to investigate the potential risk of sulfites use.[1] Controlling reactions to sulfites by avoiding sulfite use remains challenging due to their widespread use.[9] We educated our patient to check the components of drugs on the package insert, compulsorily before use.[4]

In conclusion, we report the first case of erythroderma caused by sodium bisulfite via delayed-type hypersensitivity reaction, which was diagnosed by the 1% patch test. We also observed cross-reactivity between sodium bisulfite and sodium metabisulfite.

*Conflict of interest*

The authors have no conflict of interest to declare.

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Received 10 September 2020
Received in revised form 22 December 2020
Accepted 4 January 2021
Available online 18 February 2021