Adverse reactions caused by metabisulfites, with particular emphasis on contact allergy – a study of 396 patients and review of literature

ADRIANA POLAŃSKA, DOROTA JENEROWICZ, MARIA ŻMUDZIŃSKA, ALEKSANDRA DAŃCZAK-PAZDROWSKA, MAGDALENA CZARNECKA-OPERACZ, WOJCIECH SILNY

Department of Dermatology, Poznan University of Medical Sciences, Poznań, Poland

Abstract
Sulfur compounds, especially metabisulfites, are ubiquitous, widely used preservatives for many applications. They are commonly used in food as well as in pharmaceutical and cosmetic industries. There are numerous reports indicating the important role of metabisulfites as occupational allergens, causing allergic contact dermatitis mainly involving hands. The aim of this paper is to review the recent data on adverse reactions caused by these compounds with particular emphasis on contact allergy. The authors also present their own results of patch tests with sodium metabisulfite.

Key words: metabisulfites, contact allergy to sulfites, anesthetics.

Introduction
Inorganic sulfur compounds, such as sulfur dioxide (SO₂), potassium and sodium bisulfate (KHSO₃; NaHSO₃), potassium and sodium metabisulfite (K₂S₂O₅; Na₂S₂O₅), are ubiquitous, widely used preservatives for many applications [1]. They are commonly used in food industry (as antioxidants, preservatives and agents to prevent browning), as well as in pharmaceutical and cosmetic industries [1, 2]. With so many applications, in the 70’s of last century, the relationship between exposure to metabisulfites and the possible adverse reactions, was recognized [3]. The available literature data provide much information on a variety of adverse effects due to their oral, parenteral and local exposure. Cutaneous manifestations such as urticaria and contact dermatitis, also well-documented attacks of asthma, abdominal pain and diarrhea, as well as hypotension, even followed by fully developed anaphylactic shock have already been described. Given the wide range of possible symptoms provoked by sulfites, their etiology is still not fully understood and the involvement of different mechanisms are postulated [1-3].

In 1968, Nater et al. described one of the first cases of allergic contact dermatitis caused by potassium metabisulfite in an employee of a pharmaceutical company [4]. Since that time, numerous reports on the positive patch tests’ results with metabisulfites have been published. Because of the widespread occurrence of sulfur compounds, their relevance is often difficult to evaluate [5-7]. However, the possibility of an occupational allergy to metabisulfites has been clearly highlighted [8].

The aim of this paper is to review recent data on adverse reactions caused by metabisulfites with particular emphasis on contact allergy. The authors also present their own results of patch tests with sodium metabisulfite performed in a group of patients diagnosed and treated in the Department of Dermatology Poznan University of Medical Sciences in Poznań, Poland.

Occurrence of sulfiting agents
As mentioned above, the sulfites are widely used in various industries, and therefore a possible occupational exposure to these substances should be expected. In most cas-
es, exposure to that group of compounds is oral. As synthetic food additives known as E223, E224, metabisulfites reduce enzymatic and nonenzymatic browning process [2, 3]. Antioxidant properties of these agents cause inhibition of the excessive growth of bacteria in bottled soft drinks, wine or beer and frozen dough (pizza). They are widely used not only for wine production, but also in the process of wine equipment disinfection. The food products containing sulfites are presented in Table 1 [2, 3]. In 1985, the U.S. Food and Drug Administration (FDA) banned the use of sulfites in fresh fruits and vegetables, but it is still allowed to use them in other products, and beverages. The highest levels of these additives can be found in dried fruits (values exceeding 1000 ppm (parts per one million)), while the lowest (below 10 ppm) in frozen dough, and jelly. It is worth emphasizing that Saccharomyces cerevisiae, fermenting yeast used in the production of beer and wine, also produces SO₂ reaching the level up to 30 ppm [1-3].

Another possible way of exposure to metabisulfites constitute cosmetics, particularly hair care products and dyes, also perfumes, tanning preparations and the whole range of cleansers and skin moisturizers (Table 1) [2, 9-11]. These compounds are also widely used in photographic industry as fixers [5]. Thanks to the property to prevent oxidation, discussed agents are added to many drugs used either topically, orally or parenterally. Compared with food products, pharmaceuticals contain small quantities of sulfites (from 0.25% to 1.0%) [3]. Local anesthetics with epinephrine are one of the essential medicines that contain sulfur additives. Moreover, isoproterenol, a ‘historical bronchodilator’, was previously an important source of these compounds. It should also be mentioned, that antifungal creams and topical formulations in the treatment of hemorrhoids, also eye drops with sympathomimetics, and numerous solutions for intravenous infusion may contain sulfites (Table 1) [2, 3, 12].

**Clinical manifestations of hypersensitivity to sulfites**

It is well known that bronchospasm in asthmatic patients may be caused by inhalation of SO₂ and its relationship to ambient air pollution has been proven [13]. However, asthma associated with sensitivity to sulfites is defined as the occurrence of typical symptoms after consumption of foods containing these compounds, and it is estimated that this relationship occurs in 3-10% of asthmatics [2, 14]. The first report suggesting that association was published in 1973 [15], while three years later, the occurrence of anaphylaxis after eating salad containing sodium metabisulfite was reported (Table 2) [16]. In subsequent years, there have been numerous papers published on adverse reactions associated with consumption of foods containing sulfites in patients with asthma. Most of them reported attacks of dyspnea and cough [14], in addition there are isolated reports of abdominal pain and diarrhea [17], as well as urticaria and angioedema [18]. The clinical features of asthmatics with hypersensitivity to sulfites were defined in 1981 and these are cases of chronic and steroid-dependent types of the disease with coexistence of rhinosinusitis [2]. The pathomechanism of hypersensitivity to sulfites in asthma is not clearly defined. It seems that bronchoconstriction is due to the formation of SO₂, which causes increased cholinergic reflex, both by ingestion and inhalation. Similarly, urticaria, angioedema, and abdomi-
Adverse reactions caused by metabisulfites, with particular emphasis on contact allergy – a study of 396 patients and review of literature

The possibility of developing a type IV hypersensitivity reaction in relation to sulfites was reported in 1968 [4]. Many studies evaluated the incidence of allergy and attempted to determine its actual relevance. According to published data, the incidence of positive patch test results with metabisulfites ranges from 1.4% to 4%, but only few authors have been able to prove the true relationship between positive result of test and exposure to this allergen (Table 2) [5-7].

We examined 396 patients treated and diagnosed in the Department of Dermatology, Poznan University of Medical Sciences in Poznań. All of the patients, due to the suspicion of possible contact allergy were patch tested with European standard set of contact allergens broadened by 1% sodium metabisulfite (pet.). Patch tests’ protocol fulfilled recommendations and guidelines of the Allergy Section of the Polish Society of Dermatology. The readings were performed according to the rules of the International Group Contact Dermatitis Research Group (ICDRG). In order to evaluate the clinical significance of allergy in patients with positive test results with sodium metabisulfite,

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Methodology</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patch test (potassium metabisulfite 1% and 5% aq.)</td>
<td>Positive</td>
<td>Nater JP, 1968 [4]</td>
</tr>
<tr>
<td>1</td>
<td>Skin prick test Intradermal test (10 mg/mL sulfite bisulfite)</td>
<td>Positive</td>
<td>Premer BM, et al., 1976 [16]</td>
</tr>
<tr>
<td>1762</td>
<td>Patch test (sodium sulfite 1% pet.)</td>
<td>1.4% Positive</td>
<td>Petersen C and Menné T, 1992 [6]</td>
</tr>
<tr>
<td>1</td>
<td>Patch test (sodium metabisulfite 2% pet.)</td>
<td>Positive</td>
<td>Riemersma WA, et al., 2004 [23]</td>
</tr>
<tr>
<td>1751</td>
<td>Patch test (sodium metabisulfite 1% pet.)</td>
<td>4.1% Positive</td>
<td>Madan V, et al., 2007 [7]</td>
</tr>
<tr>
<td>1</td>
<td>Skin prick test (1%) Intradermal test (0.1%)</td>
<td>Positive</td>
<td>Stingeni L, et al., 2009 [22]</td>
</tr>
<tr>
<td>1</td>
<td>Patch test (potassium metabisulfite 1% pet., sodium metabisulfite 1% pet., sodium sulfite 1% pet.)</td>
<td>Positive</td>
<td>Riemersma WA, et al., 2004 [23]</td>
</tr>
<tr>
<td>1</td>
<td>Patch test</td>
<td>Positive</td>
<td>Sasseville D and El-Helou T, 2009 [8]</td>
</tr>
<tr>
<td>1</td>
<td>Skin prick test (10 mg/mL metabisulfite) Double blind placebo controlled sulphite provocation test (with sodium metabisulfite) Basophil activation test (5.21 and 20.8 µg/ml sodium metabisulfite)</td>
<td>Negative</td>
<td>García-Ortega P, et al., 2010 [20]</td>
</tr>
<tr>
<td>1518</td>
<td>Patch test (sodium metabisulfite 2% in pet.)</td>
<td>3.4% Positive</td>
<td>Kaaman AC, et al., 2010 [21]</td>
</tr>
</tbody>
</table>

Contact allergy – own experience and review of literature data

The possibility of developing a type IV hypersensitivity reaction in relation to sulfites was reported in 1968 [4]. Many studies evaluated the incidence of allergy and attempted to determine its actual relevance. According to published data, the incidence of positive patch test results with metabisulfites ranges from 1.4% to 4%, but only few authors have been able to prove the true relationship between positive result of test and exposure to this allergen (Table 2) [5-7].

We examined 396 patients treated and diagnosed in the Department of Dermatology, Poznan University of Medical Sciences in Poznań. All of the patients, due to the suspicion of possible contact allergy were patch tested with European standard set of contact allergens broadened by 1% sodium metabisulfite (pet.). Patch tests’ protocol fulfilled recommendations and guidelines of the Allergy Section of the Polish Society of Dermatology. The readings were performed according to the rules of the International Group Contact Dermatitis Research Group (ICDRG). In order to evaluate the clinical significance of allergy in patients with positive test results with sodium metabisul-
Adriana Polańska et al.

One of the first reports of occupational airborne contact dermatitis caused by sodium metabisulfite in a 37-year-old man working on the production of wine. The patient presented erythematous and scaly lesions within the face and forearms and seasonally relapsed during the grape harvest. Patch tests were positive with sodium and potassium metabisulfite, interestingly, there was also a positive delayed eczematous reaction to prick and intradermal tests with sulfites.

In local anesthetics, particularly those containing sympathomimetics sulfites are also present [2, 12, 23]. It is estimated that only about 1% of adverse reactions to local anesthetics have ‘true’ allergic etiology, whereas more often the symptoms can be caused by additives such as antioxidants (sulfur compounds) [24, 25]. Dutch researchers [23] reported the occurrence of a delayed reaction in a patient who received local anesthetic injection (lidocaine 2% with adrenaline) for a biopsy of a suspected basal cell carcinoma. According to the patient, burning sensation developed around the site of injection after 7 hr, itch after 24 hrs, whereas after 48 hrs erythema and edema were observed. Dooms-Goossens et al. [12] presented another case of a patient, who was injected with lidocaine with epinephrine in order to perform a dental pain-free procedure. After 2 hours swelling of the face and neck were observed. Both cases of hypersensitivity in relation to sodium metabisulfite have been confirmed with patch tests. There are also data suggesting another mechanisms involved in the development of skin lesions in relation to local anesthetics containing sulfur compounds. A report from 1985 showed generalized eruptions of wheals after novocaine anesthesia with epinephrine [26]. In the presented case, the prick and intradermal test with sulfur compounds were negative, however oral bisulfate challenge caused an urticarial response.

Conclusions

Possible side effects of metabisulfites are a frequent subject of literature reports, suggesting that these compounds are of important clinical significance. Wide variety of sensitivity reactions to the discussed agents, possibility of provoking similar symptoms as a result of different routes of exposure, points to the complex, not fully elucidated mechanism of hypersensitivity. Undoubtedly, in patients with positive patch tests and eczematous skin lesions, the possible mechanism involves type IV hypersensitivity reaction according to Gell and Coombs. On the other hand, anaphylaxis, urticaria and angioedema as well as rhinoconjunctivitis may suggest immediate hypersensitivity, but exactly IgE-mediated reactions were confirmed only in few cases. Possibly, pseudoallergic mechanism or nonspecific stimulation of mast cells by sulfites is responsible for other cases. Similarly, in asthmatic patients bronchospasm has been associated with refractory activation of cholinergic system by sulfites. Clinicians should bear in mind potential sources of exposure, with particular emphasis on professional contacts, as well as drugs, including local anesthetics.
Adverse reactions caused by metabisulfites, with particular emphasis on contact allergy – a study of 396 patients and review of literature

References