Review paper

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

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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.*

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Introduction

Inorganic sulfur compounds, such as sulfur dioxide (SO_2), potassium and sodium bisulfate ($KHSO_3$; $NaHSO_3$), potassium and sodium metabisulfite ($K_2S_2O_5$; $Na_2S_2O_5$), 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-

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Table 1. Overview of the most common food products, pharmaceuticals and cosmetics that contain sulfur compounds

Food products	Drugs	Cosmetics
apricots, raisins *(et al*. dried fruit)	antifungal creams/ointments	hair dyes and bleaches
avocado (*et al*. fresh fruits)	glucocorticoid creams/ointments	bronzers
beer, malt beer, wine	local anesthetics	face creams, eye creams
beet sugar	adrenaline	bubble baths
canned food (seafood in the can, soup in a can)	isoprenaline	hair sprays
cider	glucocorticoids administered by injection	perfumes
gelatin (*et al*. jelly)	dopamine	make-up products
lemon juice	propofol	
fries, pizza	doxycycline	
salad (especially given the restaurant)	aminoglycoside antibiotics	
vegetables wrapped in foil	vitamin B complex	
vinegar		
sausage		

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 SO_2 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, isoprotenerol, a 'historical bronchodilatator', was previously an important source of these compunds. 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 SO_2 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 SO_2, which causes increased cholinergic reflex, both by ingestion and inhalation. Similarly, urticaria, angioedema, and abdomi-

Table 2. Literature review

Number of patients	Methodology	Results	References
1	Patch test (potassium metabisulfite 1% and 5% aq.)	Positive	Nater JP, 1968 [4]
1	Skin prick test Intradermal test (10 mg/mL suffite bisulfite)	Positive Positive	Prenner BM, *et al*., 1976 [16]
1762	Patch test (sodium sulfite 1% pet.)	1.4% Positive	Petersen C and Menné T, 1992 [6]
2894	Patch test (sodium metabisulfite 1% pet.)	1.7% Positive	Vena G, *et al*., 1994 [5]
1	Patch test (sodium metabisulfite 2% pet.) Skin prick test (sodium metabisulfite 0.05%, 0.1%, 1%, 10%)	Positive Negative	Riemersma WA, *et al*., 2004 [23]
1751	Patch test (sodium metabisulfite 1% pet.)	4.1% Positive	Madan V, *et al*., 2007 [7]
1	Skin prick test (1%) Intradermal test (0.1%) Patch test (potassium metabisulfite 1% pet., sodium metabisulfite 1% pet., sodium sulfite 1% pet.)	Positive Positive Positive to potassium and sodium metabisulfite	Stingeni L, *et al*., 2009 [22]
1	Patch test	Positive	Sasseville D and El-Helou T, 2009 [8]
1	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)	Negative Positive Positive	García-Ortega P, *et al*., 2010 [20]
1518	Patch test (sodium metabisulfite 2% in pet.)	3.4% Positive	Kaaman AC, *et al*., 2010 [21]

nal discomfort in these patients is explained by the generation of SO_2 in the stomach. Among other reasons, reports on possible sulphite oxidase deficiency have been also presented [2, 3].

Clayton and Busse described a female with a negative personal history of atopic diseases who has experienced life-threatening anaphylactic reaction associated with a massive eruption of wheals after consumption of wine [19]. Similar reports can be found in recent reports (2010) [20]. Spanish researchers published a case report of a 56-year-old man, also with a negative history of atopy, who after drinking wine presented itching ears, conjunctivitis and angioedema of the lips with concomitant urticaria. The patient was diagnosed, including skin prick tests with sodium metabisulfite, which were negative, however double-blind-placebo-controlled provocation test with 10 mg dose of sodium metabisulfite provoked symptoms of urticaria and pruritus. In addition, the basophil activation test (BAT), revealed strong positive result [20]. There are only a few reports that present a positive skin prick test results and/or intradermal tests with sulfites in patients with suspected hypersensitivity to the discussed agents [16]. It seems that occurrence of typical IgE-mediated reactions in this group of patients is very rare [3].

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-

fite, detailed clinical history on a possible occupational and nonoccupational contact with the allergen were taken. Particular attention in these patients was paid to the occurrence of adverse reactions during minor surgery with local anesthetic.

Patch test were positive in 198 patients (50%), while positive response in relation to sodium metabisulfite was observed in 26 patients (13.1%). The ratio of female to male was 1 : 1. Among subjects with contact allergy to sodium metabisulfite, the most frequently observed skin symptoms were hand dermatitis and generalized pruritus. However some patients, reported eruption of wheals and allergic conjunctivitis. Three patients (11.5%) of 26, associated the skin lesions with dental surgery performed with local anesthesia, while 9 patients (34.6%) reported worsening of skin lesions after ingestion of wine, and 6 (23.1%) after consumption of fresh fruit. Another 6 patients (23.1%) complained about exacerbation of skin after bathing in the pool. None of the patients reported possible occupational exposure associated to sodium metabisulfite.

Results presented above suggest the frequent occurrence of contact allergy in relation to metabisulfites, however, as reported by other authors, not in all cases its connection with the true exposure can be shown. Due to its ubiquitous nature, identification of sodium metabisulfites' source may cause difficulties. Similar problems in assessing the relevance of contact allergy existed in the past, for example in relation to thiomersal [21].

Madan *et al*. [7] reported positive patch tests' results with sodium metabisulfite in 4.1% of cases, of which 46.5% have documented the clinical relevance of allergy. In 16 cases researchers have demonstrated significant correlation to the occupation. However, the most common nonoccupational source of allergen in this study were topical medications. Also in the presented report, similarly to our results, skin lesions were located mainly within the hands. In another study published in 1994 [5], contact allergy caused by sodium metabisulfite was revealed in 50 patients out of 2,894 tested. However, only in 12 cases the reaction was considered as clinically significant and most frequently occupational allergens were responsible for it (in 7 patients). According to available literature data, positive reactions with metabisulfites are observed mainly in bakers, photographers, food industry workers (preparing salads and health care workers exposed to local anesthetic agents) [8, 21]. There are reports of occupational allergy to discussed compounds also in hairdressers as well as carpenters [7, 12]. Skin lesions in these patients are localized mainly within the hands. Stingeni *et al*. [21, 22] presented 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 reactions 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 (sulphur 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 eprinephrine 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 have 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.

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