

Sodium metabisulfite hypersensitivity in urticaria

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ABSTRACT

Background: Sodium metabisulfite is a recognized, but rare, trigger of urticaria, wherein the IgE mechanism has been sporadically proven. The aim of this study was to identify the potential reaction to sodium metabisulfite (MBS) based on a placebo-controlled oral challenge in patients with urticaria and suspected hypersensitivity to food additives. **Materials and Methods:** A total of 110 adult patients (76 females and 34 males with a mean age of 46 years) were included in the study between 2017 and 2019. All subjects underwent MBS skin prick tests (SPT) and patch tests (PT). Patients with a positive skin test or suspected MBS hypersensitivity were qualified for a placebo-controlled oral challenge (OC). **Results:** Skin testing was positive in 24 patients: SPT in 20% (n = 22), PT in 5% (n = 6). Out of 64 oral challenges, 13 positive results were obtained. Patients with a positive challenge typed sulfite foods twice as often as a culprit compared to those with a negative OC. **Conclusions:** In patients with urticaria, both the IgE and non-IgE mechanism of MBS hypersensitivity has been demonstrated. Skin tests with a detailed medical history of potentially guilty foods may be helpful in determining sulfite hypersensitivity.

Key words: Sulfites; Sodium metabisulfite; Urticaria; Food additive hypersensitivity

INTRODUCTION

Sulfites are a group of inorganic salts that, in a certain environment, liberate sulfur dioxide. A range of them—such as sodium and potassium metabisulfite, sodium sulfite, and sodium and potassium bisulfite—are used in the food, beverage, cosmetic, medicine, rubber, and photographic industry as a preservative and a bleaching and antioxidative agent [1-3]. They are key preservatives of wine, beer, grapefruit juice, dried fruits, and seafood and are widely used in the production of processed foods [4-6]. The acceptable daily intake (ADI) for sulfites, in terms of sulfur dioxide, is 0.7 mg per 1 kg of body weight per day, but their intake is often exceeded. According to the European Union regulation, the total amount of sulfur dioxide in wine must not exceed 150 mg/L for red wines and 200 mg/L for white and rose wines, and is higher for sparkling and sweet wines (up to 235 and 400 mg/L respectively). Although producers are obliged to label products with a sulfite concentration of over 10 mg/L appropriately,

they are not obliged to disclose the total amount of the substance [5].

The hypersensitivity symptoms described after sulfites ingestion may include rhinitis [7], asthma [6,8-10], urticaria [11-13], systemic rash [14-16], intestinal disorders, dizziness [7], headache [17], and anaphylaxis [7,18-20]. Sulfites are thought to be the main food additive exacerbating asthma, which affects 3–10% of the population [20]. Numerous studies have reported sensitization to take place through the skin, for instance, after the application of an anti-fungal or anti-hemorrhoid medicine, hair dye, or facial cream or after contact with animal feed, caused by prolonged occupational exposure [7,20]. Contact allergy is also a proven and well-known sulfite side effect [1,7,21-23].

The mechanisms lying behind these reactions are only partially known [24]. Some of the patients may not be able to metabolize sulfiting agents well enough due to a deficiency of the enzyme sulfite oxidase, which

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may lead to hypersensitivity symptoms [9,20]. An interesting thesis is the possibility of suppression of the Th1-type immune response by sulfites, resulting in the advantage of the Th2 mechanism [25]. The immunological background of the reaction has been proven in some cases [26], but other authors question this link [4].

Several observations indicate that the asthma phenotype is more common than urticaria in sulfite hypersensitivity [5,8,9]. The subject of the present study was to assess the frequency of sodium metabisulfite hypersensitivity in patients with urticaria and suspected hypersensitivity to food additives, with an identification of the IgE and non-IgE dependent reactions.

MATERIALS AND METHODS

Patients

The study included patients with a duration of urticaria of more than six weeks, hospitalized with a suspicion of hypersensitivity to food additives, at the Department of Allergology of the Medical University of Gdańsk, Poland, between 2017 and 2019. A group of 110 patients was qualified for the study (Table 1). Before hospitalization, all participants completed a detailed questionnaire regarding the duration and nature of urticaria, eating habits, the use of an elimination diet, the allergy diagnostics performed, as well as the assessment of the effectiveness of the current treatment.

Patients had not been taking antihistamines for seven days and systemic glucocorticoids for one month prior to hospitalization. Spirometry was performed for any coexisting asthma or chronic obstructive pulmonary disease. Written consent was obtained. The study protocol was approved by the local bioethics committee (NKBBN/546/2016-2017) and was in line with the principles of ethics and the Declaration of Helsinki.

Skin Testing

All patients underwent MBS skin tests. Sodium metabisulfite from Euro-Win Ltd., Jaslo, Poland, was used in the study. To prepare SPTs, it was diluted with saline and glycerol at a 1:1 ratio to obtain a 1% solution (i.e., a concentration of 10 mg/mL). A positive and negative control was performed (histamine hydrochloride 10 mg/mL and saline from Allergopharma). A wheal diameter of a minimum

Table 1: Patient characteristics.

Number of patients	n = 110
Average age (in yrs.)	46.1
Females / males	69% / 31%
Atopy	64.6%
Asthma	22.7%
Systemic symptoms	56.4%
Past use of glucocorticoids	42.7%
Adrenaline prescription	40.9%
Manifestation of urticaria	Urticaria + angioedema 50.9%
	Urticaria only 32.7%
	Angioedema only 16.4%
Duration of disease	Average duration (in yrs.) 7.2
	Up to 5 years 53.6%
	More than 5 years 46.4%
Onset of symptoms*	More often at night 26.4%
	Until noon 4.6%
	In the afternoon 19.1%
	Other 58.2%
Symptoms location*	Face 83.6%
	Hands 36.4%
	Forearms and arms 52.7%
	Trunk 52.7%
	Feet 34.6%
	Legs 39.1%
	Genitals 20.9%
AH1 treatment efficacy	Good 22.7%
	Partial 35.5%
	Bad 41.8%

* Multiple responses were allowed.

of 3 mm with surrounding erythema larger than the negative control and representing the average of the two largest perpendicular dimensions was considered positive. A negative MBS SPT was obtained in 100 patients from the control group without urticaria who were consulted at the outpatient clinic.

Patch tests were performed with commercial sodium metabisulfite (S-011, Chemotechnique Diagnostics, Vellinge, Sweden), and MBS on a petrolatum vehicle prepared by the pharmacy, both in a 1% concentration. The tests were performed using IQ-Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden) and rated on days D2, D3, D4, D5, D6, and D7. Readings were performed according to the International Contact Dermatitis Research Group criteria. Some of the readings were carried out on an outpatient basis. An intravenous line single-blind oral challenge with MBS was then performed.

Oral Challenge

Patients with any positive skin test or a history suggesting the possibility of sulfite hypersensitivity were qualified for a single-blind placebo-controlled

oral challenge. OCs were performed according to the following protocol: placebo, 10 mg, 20 mg, and 100 mg capsules were administered in 30-minute intervals, followed by 200 mg after two hours. After the last dose, the patients underwent a minimum of two hours of observation, and immediate contact with the hospital was recommended within the next 24 hours should any symptoms appear. A test was considered positive according to objective symptoms, such as urticaria, angioedema, conjunctivitis, rhinitis, and bronchoconstriction confirmed in spirometry within 24 hours after the challenge. In the case of a hypersensitivity reaction, the participants were given antihistamines, glucocorticoids, and intramuscular adrenaline as needed.

Statistical Analysis

The significance of the association among variables was analyzed with a chi-squared test and Fischer's exact test. *P* values below .05 were considered significant.

RESULTS

Questionnaire

Almost every second patient (48%) experienced symptoms less than once a month, while 16% reported the frequency of urticaria from eight to thirty days. Based on this data and on medical history, we classified 65% of the cases as chronic inducible urticaria (CindU), 57% as chronic spontaneous urticaria (CSU), and 22% into the CindU + CSU group. Atopy, defined as a minimum of one positive skin prick test or serum IgE for airborne or food allergens, was established in 65% of the subjects. Seventy percent of the patients were convinced that it was the food that caused the symptoms. The following foods, potentially with sulfites, were listed as guilty by 24 patients before the study: wine, beer, dried fruits, olives, cakes, herring fillets, and restaurant meals.

Skin Prick Test (SPT)

A positive sodium metabisulfite SPT was obtained in 20% of the participants (MBS SPT (+), *n* = 22), among which one result was prolonged with a maximum skin reaction observed only after 3.5 hours (Fig. 1). Unlike the MBS SPT (-) patients, no statistically significant difference in sex, asthma, and atopy prevalence was observed in the MBS SPT (+) patients. The location

of urticarial symptoms was more common in the lower limbs in the MBS SPT (+) patients than in the MBS SPT (-) (59 vs. 34%, *p* < .032). Out of the 20 patients with a positive skin prick test, the oral challenge was positive in 40% (*n* = 8, *p* < .009).

Patch Test (PT)

Although patch tests are not a feasible test for the diagnosis of urticaria *per se*, they may show evidence of concomitant type I and type IV allergy reactions. A positive patch test (MBS PT (+)) was noted in six patients (5.5%; 5 females and 1 male). The tests were positive on D3 through D5 in all six patients and up to D7 in two. The results were similar on both vehicles, commercial and pharmacy prepared (Fig. 2). All six patients had a history of angioedema and urticaria, and three of them suffered from throat edema in the

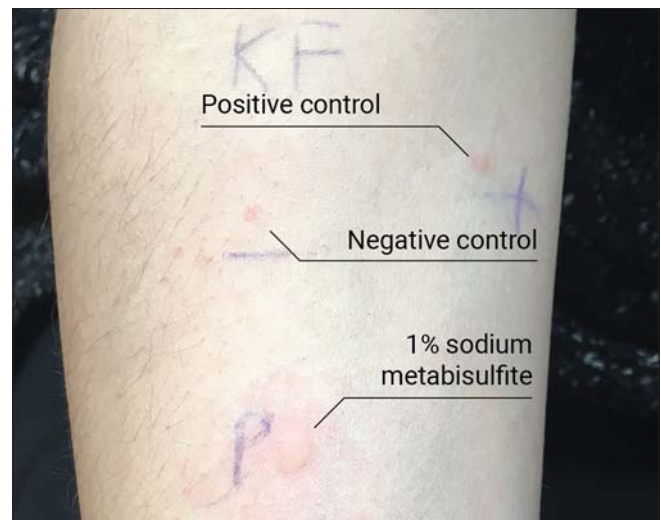


Figure 1: Sodium metabisulfite (MBS) skin prick test (SPT) after 3.5 hours.



Figure 2: Positive sodium metabisulfite patch tests (PT) (a) after 48 hours and (b) after 120 hours.

past. In this group, next to the typical facial location, compared to the group with a negative patch test, urticaria symptoms more often affected the hands (83% vs. 34%; $p < .015$), feet (83% vs. 32%; $p < .012$), and genitals (67% vs. 18%; $p < .013$). This group was dominated by people over 50 years of age and their complaints had persisted for over five years ($n = 5$; 83%). In addition, as many as five patients had used parenteral glucocorticoids (83% vs. 40%; $p < .039$). In this group, the sodium metabisulfite SPT was positive in four subjects (67%; $p < .033$), and the challenge test was positive in 2 out of the 6 patients.

Oral Challenge (OC)

An oral challenge with sodium metabisulfite was carried out in 64 out of the 110 patients. Two MBS SPT (+) patients were not challenged; one refused to participate while the other had contraindications (forced expiratory volume in one second (FEV1) below 70%). A positive result was obtained in 13 patients (MBS OC (+)).

Reactions occurred with 10 mg, 20 mg, 100 mg, and 200 mg doses in one, three, four, and five patients, respectively. These included urticaria, angioedema, rhinoconjunctivitis, shortness of breath not supported by spirometry, flatulence, pruritus, tachycardia, headache, and weakness (Table 2). All these patients were treated with a double antihistamine dose (prednisone in three and intramuscular adrenaline in two). All objective symptoms resolved within two hours of intervention.

Unlike the MBS OC (-), the MBS OC (+) patients slightly more often indicated that the food was the culprit (92% vs. 74%; $p < .17$), including 46% with complaints about food containing potential sulfites. A subsequent analysis of the causative agents reported in the questionnaires showed that the MBS OC (+) patients, unlike the MBS OC (-), more often indicated that physical exertion induced urticaria (38% vs. 12%; $p < .023$). Alcohol, stress, heat, dermatographism, infection, prolonged pressure, water, sweating, vibrations, sex cycle, and drugs were similarly often a reaction cofactor in both groups, while cold and UV radiation were slightly more often indicated as the cofactor (23% vs. 10% in both groups; p insignificant). The MBS SPT was positive in 62% of the patients with a positive challenge, and only in 24% of those with a negative challenge ($p < .009$).

DISCUSSION

In our study, we determined that hypersensitivity to sodium metabisulfite occurred in 12% of the studied patients with urticaria and suspected to have hypersensitivity to food additives. We confirmed that the clinical significance of sulfites is underestimated [20].

Several mechanisms are thought to play a role in the observed sulfites hypersensitivity, but IgE mediated reactions have rarely been documented so far [11,27,28].

In the current study, we demonstrated that, in patients with urticaria and MBS hypersensitivity, the underlying IgE mechanism is as common as the non-IgE. Assuming that a positive SPT result in an MBS OC (+) patient is evidence of IgE-dependent reactions, we confirmed the allergic mechanism in 62% of the patients (8 out of the 13) with a hypersensitivity reaction to MBS.

In our study, we noted a relatively high percentage of MBS positive skin prick tests (20%) in patients with urticaria. This finding may be explained by the strict selection of patients with suspected hypersensitivity to food additives, wherein most of them suffered from CindU.

Yang et al. obtained positive skin tests with potassium metabisulfite in five patients, which correlated with three positive challenges out of four carried out among 35 patients with hypersensitivity reactions after restaurant meals, wine, or drinks [18].

Reports of hypersensitivity to sulfites in urticaria are divergent. Jimenes-Aranda et al. found hypersensitivity to sodium metabisulfite, sodium bisulfite, and potassium bisulfite in 36%, 33%, and 31% of patients, respectively [28]. Montaña García and Orea reported a positive response after an MBS challenge in 6% of patients [29]. On the other hand, Rajan et al. showed that after the administration of various food additives, including 100 mg of MBS, patients with urticaria experienced no symptoms in a double-blind challenge [30]. One's country's eating habits and the actual sulfite content in the foods available may be important. A patient from the UK was described complaining of a rash as a result of diet changes after a visit to Italy, such as the consumption of seafood, wine, grapes, and fries [15].

Table 2: Characteristics of the patients with a positive sodium metabisulfite oral challenge

No. of patients	Age	Sex (F/M)	U/AE	Drug hypersensitivity	Food as the culprit	MBS in ASST	Asthma	Atopy	MBS SPT (mm)	MBS PT	MBS dose responsible for the reaction in the OC (mg)			Onset of reaction after the final dose (minutes)	Reactions during the OC	Treatment management in the OC
											10	20	200			
1	67	F	U/AE	-	YES	-	NEG	YES	3	(-)	x		10	rhinitis, conjunctivitis, headache, weakness, mouth edema	AH1	
2	72	F	U/AE	-	YES	YES	NEG	YES	3	(-)	x		15	cheek edema, rhinitis, dyspnea, flatulence	AH1	
3	39	F	U	-	YES	-	POS	YES	6	(-)		x	40	neck/arm urticaria, generalized itchiness	AH1, GK	
4	50	F	U/AE	YES	YES	YES	NT	YES	3	(+)		x	10	face urticaria, generalized itchiness	AH1, GK, ADR	
5	21	M	U/AE	-	YES	-	NT	YES	3	(-)		x	10	weakness, face urticaria	AH1	
6	35	F	U	-	YES	-	POS	YES	3	(-)		x	15	neck urticaria	AH1	
7	30	F	U/AE	-	YES	YES	POS	YES	4	(+)		x	120	generalized urticaria and itchiness	AH1	
8	30	F	U/AE	-	YES	YES	POS	YES	3/6*	(-)		x	120	arms/trunk urticaria	AH1	
9	44	F	U/AE	-	YES	YES	NEG	YES	0	(-)		x	10	face/cleavage urticaria, HR 90/min, feeling hot	AH1	
10	47	F	U/AE	YES	YES	-	POS	YES	0	(-)		x	5	face urticaria, cleavage urticaria (next 20 mg dose)	AH1	
11	60	F	AE	YES	-	-	NT	YES	0	(-)		x	10	tongue edema	AH1, GK, ADR	
12	24	M	U	-	YES	-	POS	YES	0	(-)		x	120	trunk/arms urticaria	AH1	
13	39	M	U/AE	YES	YES	YES	NEG	-	0	(-)		x	7h	trunk/thigh urticaria	AH1	

F - female; M - male; U - urticaria; AE - angioedema; MBS - sodium metabisulfite; ASST - autologous serum skin test; SPT - skin prick test; PT - Patch test; OC - oral challenge test; Neg - negative result; Pos - positive result, NT - not tested; * result after 30 minutes and 3.5 hours; AH1 - antihistamines; GK - glucocorticoids; ADR - adrenaline; hrs - hours

Table 3: Skin prick test and patch test sensitivity and specificity in patients with sulfite hypersensitivity

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-	OR	95% CI
SPT	61.5	76.5	40.0	88.6	2.62	0.50	5.2	1.43 - 18.91
PT	15.4	92.2	33.3	81.0	1.96	0.92	2.1	0.35 - 13.18
SPT or PT	61.5	72.6	36.4	88.1	2.24	0.53	4.2	1.18 - 15.14
SPT and PT	15.4	96.1	50.0	81.7	3.92	0.88	4.4	0.56 - 35.17

PPV - positive predictive value; NPV - negative predictive value; LR - likelihood ratio; OR - odds ratio; SPT - skin prick test; PT - patch test

Asero described a thirty-year-old female, in whom severe pruritus was observed after four hours of the administration of 10 mg sodium metabisulfite [31]. In our study, paroxysmal pruritus associated with urticaria was also the main ailment in a thirty-year-old female patient (No. 7), who was refractory to treatment even with four antihistamines tablets daily. After stopping consuming muesli with dried fruits for breakfast, she gradually reduced the treatment to only one tablet per week. Our study showed that subsequent sulfite elimination correlated with the improvement of urticaria in five patients with a positive challenge.

According to the European Food Safety Authority (EFSA), the most sulfite-sensitive individuals may show reaction to ingested metabisulfite in quantities ranging from 20 mg to 50 mg [5]. Reports show that a single restaurant meal may contain 20–200 mg of sulfites [32], and their prohibited addition to products, such as lettuce or fruit salads, has been demonstrated [18,20]. The present study observed mouth edema with rhinitis, conjunctivitis, and headache in female patient No. 1 with asthma and a positive MBS SPT, occurring within 10 minutes of administering a 10 mg dose of MBS. In addition, tearing, watery nasal discharge, and mild shortness of breath were seen up to 10 minutes after the application of a skin prick test, with the symptoms resolving spontaneously after 30 minutes; the patient had an associated airborne reaction after the exposure to sodium metabisulfite.

The results of the current study may be compared to those obtained by Ban et al. [9], who used doses ranging from 40 mg to 200 mg for the oral challenge. The authors showed that, in the group with urticaria and MBS hypersensitivity, the dose causing wheals during a challenge was, on average, 188 mg after 100 minutes of the first dose. Our study determined that the average dose followed by symptoms was 113 mg, with the reaction time of 164 minutes of the first dose of MBS.

We ascertained a percentage of 5.5% (n = 6) of positive sodium metabisulfite PTs, which was consistent with

other studies (2.2–7%) performed in the last ten years [3,7,33–35]. As the reaction was more prominent on D3 and D4 than on D2, we excluded irritancy. Similarly to some studies [20], we detected more positive MBS patch tests in females than males (5:1 ratio). However, we were not able to establish the primary source of sulfite sensitization.

We noticed that urticarial symptoms were relatively more severe in the MBS PT (+) patients and lasted longer than in the rest. Similarly to other studies [7,11], we determined that the patients with sulfite contact allergies may also have shown symptoms after their ingestion and that patch tests may be useful to diagnose immediate reactions to sulfite-containing foods [7,20]. Our study found two patients (No. 4 and 10) with a positive sodium metabisulfite SPT, PT, and challenge test. Table 3 shows the sensitivity and specificity of skin tests, wherein a positive oral challenge was regarded as the gold standard.

No group with a positive MBS test differed in terms of the coexistence of allergic rhinitis, dermatitis, asthma, or drug hypersensitivity. We found that sulfite hypersensitivity usually accompanies other allergic diseases and is rarely an isolated complaint.

Our study concluded that sodium metabisulfite hypersensitivity appears often enough to be screened in chronic urticaria and that more than half of the diagnosed urticarial cases were IgE-dependent reactions, sometimes coexisting with positive sodium metabisulfite patch tests.

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Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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