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REVIEW

Clinical effects of sulphite additives

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Summary

Sulphites are widely used as preservative and antioxidant additives in the food and pharmaceutical industries. Topical, oral or parenteral exposure to sulphites has been reported to induce a range of adverse clinical effects in sensitive individuals, ranging from dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhoea to life-threatening anaphylactic and asthmatic reactions. Exposure to the sulphites arises mainly from the consumption of foods and drinks that contain these additives; however, exposure may also occur through the use of pharmaceutical products, as well as in occupational settings. While contact sensitivity to sulphite additives in topical medications is increasingly being recognized, skin reactions also occur after ingestion of or parenteral exposure to sulphites. Most studies report a 3–10% prevalence of sulphite sensitivity among asthmatic subjects following ingestion of these additives. However, the severity of these reactions varies, and steroid-dependent asthmatics, those with marked airway hyperresponsiveness, and children with chronic asthma, appear to be at greater risk. In addition to episodic and acute symptoms, sulphites may also contribute to chronic skin and respiratory symptoms. To date, the mechanisms underlying sulphite sensitivity remain unclear, although a number of potential mechanisms have been proposed. Physicians should be aware of the range of clinical manifestations of sulphite sensitivity, as well as the potential sources of exposure. Minor modifications to diet or behaviour lead to excellent clinical outcomes for sulphite-sensitive individuals.

Introduction

Sulphites or sulphiting agents such as sodium and potassium sulphite, metabisulphite, bisulphites and sulphur dioxide (SO_2) are ubiquitous compounds with a variety of commercial uses. In fact, SO_2 has been used since ancient times as a purifier and disinfectant. Burning sulphur was used by the ancient Greeks to fumigate houses, and by the ancient Romans to sanitize wine vessels [1]. The first report in the literature of the use of SO_2 as a food preservative dates back to 1664, when it was suggested that casks should be filled with cider while they still contained SO_2, to prevent spoilage [2]. The sulphite additives are now used widely in the food industry – predominantly as anti-browning agents, antioxidants and preservatives [2, 3]. They are also used extensively in the pharmaceutical industry [4] and have a number of industrial uses.

While the apparent safety of the sulphite additives led to their widespread use, reports associating exposure to sulphites with adverse reactions began to emerge during the 1970s [5, 6]. These included the triggering of anaphylactic reactions, as well as the elicitation of a wide range of symptoms, including dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhoea, although the vast majority of reports described the triggering of bronchoconstriction in asthmatic patients [7, 8]. Despite numerous studies addressing adverse responses to the sulphite additives, the clinical importance of sensitivities to these additives remains underestimated. In this paper, we review the literature regarding the clinical effects of sulphites, focusing on skin reactions and asthmatic responses.

Exposure to the sulphite additives

For the majority of people, exposure to sulphites occurs during consumption of foods and drinks that contain these additives (Table 1). Foods containing sulphites include dried fruits, dried vegetables, pickled onions and bottled soft drinks and cordials [8, 9]. The addition of

Table 1. Major types of food that may contain sulphite additives*

Drinks
Bottled soft drinks and fruit juice, cordials, cider, beer, wine (including sparkling wine)
Other liquids
Commercial preparations of lemon and lime juice, vinegar, grape juice
Fruit
Dried apricots, fruit bars
Commercial foods
Dried potatoes, gravies, sauces and fruit toppings, maraschino cherries, pickled onions, sauerkraut, pickles, maple syrup, jams, jellies, biscuits, bread, pie and pizza dough
Salads and fruit salads
Crustaceans
Meats
Delicatessen meats, mince meat, sausages
Other foods
Gelatin, coconut

*Detailed information regarding foods containing sulphite additives can be found on the *Australasian Society of Clinical Immunology and Allergy* website (http://www.allergy.org.au/content/view/128/1/) [62].

Table 2. Medical and cosmetic uses of sulphites

Cosmetics: hair colours and bleaches, home permanent solutions, skin fading/lighteners, false tan lotions, anti-ageing creams and moisturisers, facial cleansers, around-eye creams, body washes/cleansers, hair sprays, perfumes, blush, bronzers/highlighters.
Medications: Topical anti-fungal and corticosteroid creams and ointments (e.g. Trimovate®, Timodine®, Aureocort®, Aureomycin®, Nizoral®, Nystatin®, Lustra®, Psoradrate®), adrenaline, isoprenaline, isoproterenol, isoetharine, phenylephrine, dexamethasone and injectable corticosteroids, dopamine, local anaesthetics, propofol, aminoglycoside antibiotics, metoclopramide, doxycycline and vitamin B complex.

Table 3. Industrial uses of sulphites

Industry	Uses
Food and drink	Preservation and sterilization, sugar refining
Brewing, wine making	Sterilization in fermentation processes
Photographic chemicals	Formulation and protection of developers and fixers
Dyehouses, laundries	Colour stripper and anti-chlor
Leather	Tanning (acidifying agent), solubilizing agent for tannins, reducing chrome liquors
Textiles	Bleaching, desulphurizing and dechlorinating
Mineral extraction	Ore flotation aid
Pulp and paper	Water treatment, bleaching ground wood
Effluent treatment	Reduction of chromium salts
Chemical manufacture	In manufacture of sulphosuccinates and sodium formaldehyde bisulphite, a sulphonation and sulphomethylation agent
Rubber manufacture	Latex anticoagulant
Parenteral solutions	Prevention of oxidation of adrenaline
Water and sewage treatment	Disinfectant neutralization

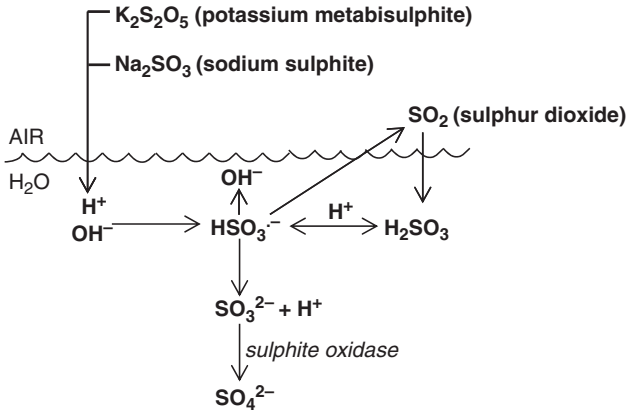

Fig. 1. Sulphite chemistry. Adapted from Stevenson and Simon [12].

sulphite additives to beer and wine is permitted in most countries, and although in many countries the use of sulphites in fresh salads, fruit salads, mincemeat or sausage meat is illegal, it may still occur. In addition to food, exposure to sulphites can occur through the use of cosmetics and medicines (Table 2). Cosmetics containing sulphites include hair colours and bleaches, creams and perfumes [10]. Medicines containing sulphites include eye drops, topical medications and parenteral medications such as adrenaline, phenylephrine, corticosteroids and local anaesthetics [4, 11]. Sulphites also have a number of industrial uses, and consequently, occupational exposures to these additives may occur (Table 3).

Sulphite salts and SO_2 establish a pH-dependent equilibrium when dissolved in water [12]. At low pH, the equilibrium favours sulphurous acid (H_2SO_3), at intermediate pH bisulphite ions (HSO_3^-) predominate, while at high pH the formation of sulphite ions (SO_3^{2-}) is favoured (Fig. 1). In addition to these 'free' sulphite species that are formed in aqueous solutions, 'bound' sulphites are also formed in foods by the reaction of sulphites with carbohydrate, protein and lipid molecules. These reactions with macromolecules in foods may or may not be reversible, and the relative proportion of free and bound sulphites varies in different foods and depends on the temperature, pH, macromolecular composition of the food and the concentration of sulphite [1, 13, 14]. The concentration of free sulphites in foods correlates with the preservative activity, with sulphite levels in foods and drinks usually expressed as theoretical yields or 'equivalents' of SO_2. In addition to their preservative activity, sulphites may be used to prevent the browning of foods, as bleaching agents, as dough conditioning agents, in preventing excess alkalinity of foods, as food processing aids, colour stabilizers and antioxidants [2, 3]. Thus, in addition to being cheap and convenient, sulphites are extremely versatile, and in many foods, serve more than one purpose.

Sensitivities to sulphite additives

Skin sensitivities

Nater [15] reported one of the first cases of contact dermatitis to sulphite in 1968. His patient was a 40-year-old woman who was exposed to potassium metabisulphite while working in the pharmaceutical industry. Wearing of gloves and avoidance of contact resulted in clearance of her hand dermatitis, but later injection of a sulphite-containing local anaesthetic for minor surgery resulted in a relapse. Subsequent patch testing confirmed sensitivity to potassium metabisulphite. Since this report, several authors have described their experience of patch testing with sulphites in order to evaluate the cause of their patients' dermatitis.

To study the prevalence of type IV allergic reactions to sodium sulphite, Petersen and Menne [16] patch tested 1762 consecutive patients with sodium sulphite. Twenty-five (1.4%) patients tested positive, but only three reactions were considered clinically relevant; that is, a relevant source of sulphite exposure was identified in the patient's domestic environment. The reason for the inability to identify the offending exposure in a large proportion of patients reacting to sulphite was unclear and although occupational exposure to sulphites was suggested as a possibility, this was not evaluated. Similarly, Vena et al. [17] patch tested 2894 eczema patients with sodium metabisulphite. Fifty (1.7%) showed positive reactions and two also tested positive to sodium sulphite. Twelve (24%) of the 50 positive reactions were considered clinically relevant, of which seven (14%) were due to occupational exposure and five (11.6%) to non-occupational exposure. Prick tests, intradermal tests and oral challenges with sodium metabisulphite were negative in these cases. However, despite the high yield of positive patch test reactions, the clinical relevance of these positive responses to challenge could not be established in most patients.

In a more recent study, Madan et al. [18] reviewed the case notes of 71 patients (4.1% of 1751 patients patch tested to sodium metabisulphite) with positive patch test responses, with a view to identifying the sources of sodium metabisulphite in these patients' occupational or domestic environments. Positive patch test reactions had been reported as relevant for 33 patients (group A), or of unexplained relevance for 38 (group B), depending on the presence or absence of identifiable sources at the time of initial reporting. Although the hands were the most common primary site of involvement in both groups, a high incidence of perianal dermatitis was observed in group A, which corresponded with exposure to sodium metabisulphite in Trimovate® (GlaxoSmithKline, Uxbridge, UK) (29.6%) and Timodine® (Forum Health Products Ltd, Redhill, UK) (15.5%) creams. Occupational exposure was considered to be a source of sensitization in seven (9.8%) group A patients and nine (12.7%) group B patients. Re-analysis to identify overlooked sources of contact increased the number of potentially clinically relevant cases from 33 to 47 (3.0% of patients tested).

In addition to patch test studies, there are a number of case reports describing adverse skin reactions following exposure to sulphite additives in various forms. Reactions following exposures to cosmetics, such as facial cosmetic creams [19], hair dyes [20] and false tanning lotion [18] have been reported. In addition, topical medications, such as antifungal [16] and haemorrhoid creams [21] and eye drops [22], have been associated with the elicitation of skin symptoms. Additionally, exposure to sulphites in swimming pool water may be relevant when considering positive patch test reactions [18]. Similarly, a wide range of occupational exposures have also been linked with adverse skin reactions to the sulphites. Reports in the literature include adverse reactions to sulphites in a photographic technician [23], pharmaceutical factory workers [15, 24], salad makers [25] and bakers [26, 27]. Occupational exposures have also been reported in a wine producer, agronomist, carpenter, chemical factory worker and hairdresser [28].

Besides topical exposure, skin reactions to sulphite additives can also occur following ingestion and parenteral exposure. One report indicated that of 36 patients with a clinical diagnosis of chronic urticaria, 36%, 33% and 30.5% showed positive oral challenge tests to sodium metabisulphite, sodium bisulphite and potassium metabisulphite, respectively [29]. There have also been case reports of sulphite-induced urticarial and anaphylactic reactions following exposure to local anaesthetics [28] and parenteral products [11, 30].

Respiratory sensitivities

The first reported case of asthma triggered by SO_2 probably dates back to the eruption of Mt Vesuvius in 79 AD, when Pliny the Elder, whose airways were 'constitutionally weak and narrow and often inflamed', collapsed and died after inhaling the sulphurous gases emanating from the volcano [31]. Most non-asthmatic individuals can tolerate up to 5 p.p.m. SO_2, whereas 20–25% of subjects with airway hyperresponsiveness (AHR) to methacholine are also hyperresponsive to SO_2 and may experience bronchoconstriction when exposed to 0.25–2 p.p.m. of SO_2 [32, 33]. Sensitivity to SO_2 is potentiated by exercise [34, 35], depends on the route of inhalation (oral vs. nasal) [36] and on the frequency of exposure, with some evidence for short-term tachyphylaxis [37]. The sensitivity of asthmatic subjects to SO_2 has been reviewed previously, particularly in relation to the effects of air pollution on subjects with airway disease [38, 39], and will not be discussed further in this review. Sulphite-sensitive asthma, which is the main focus of this review, is generally

defined as the occurrence of respiratory symptoms following the ingestion of sulphites, and it has been estimated that 3–10% of asthmatics experience such symptoms [7, 12, 40].

One of the earliest reports suggesting that ingested sulphites could cause irritation of the respiratory tract was published in 1973 [5]. Since then, numerous case reports and reviews have been published on the phenomenon of respiratory hypersensitivity to ingested sulphites. The first case of anaphylaxis following ingestion of sodium metabisulphite in a restaurant salad was reported in 1976 [6], and the following year SO_2 in orange drinks was reported to induce asthma [31]. In the early 1980s, there were numerous reports suggesting that ingestion of sulphites by susceptible individuals was the cause of severe adverse reactions. Although many of these were asthmatic responses [12, 41, 42], urticaria and angio-oedema [43], abdominal pain and diarrhoea [44], as well as anaphylaxis [45, 46] were reported. In 1985, Yang and Purchase [47] reported that there had been more than 250 cases of sulphite-related adverse reactions, including six deaths in the United States, while in Canada, 10 sulphite-related adverse reactions and one death, thought to be sulphite related, had been reported.

As a consequence of these reported adverse reactions, the US Food and Drug Administration (FDA) acted in 1986 to prohibit the use of sulphites on fruits and vegetables that were to be served raw or presented as fresh to the public. For foods and drinks in which the use of sulphite was permitted, sulphite concentrations > 10 p.p.m. had to be declared on the label [48]. Despite the introduction of these regulations, there continued to be sporadic reports of serious adverse effects following unintended ingestion of sulphites. Wüthrich and Huwyler [49] reported seven patients with pre-existing asthma and/or rhinitis, who experienced severe, life-threatening asthmatic and urticarial reactions after ingestion of wine, salads and other food that contained sulphites. Fatal asthma after consumption of sulphite-containing wine was also reported [50]. The life-threatening nature of some reactions to sulphite was further emphasized by admission to an emergency room in Sacramento, CA, of six patients who had consumed the same brand of salsa [51]. Two patients experienced exacerbations of their asthma, two experienced coughing and tightness of the throat and two required mechanical ventilation. The offending salsa was subsequently found to contain 1800 p.p.m. of sulphite.

The US FDA Center for Food Safety and Applied Nutrition has monitored reports of adverse reactions to sulphites since 1980, and as of 1999 had received 1132 reports from consumers, describing adverse reactions thought to have been caused by the ingestion of sulphite-containing foods [52]. Of 799 reported reactions for which there was adequate information, 388 (48.6%) were classified as severe. However, from 1996 through 1999, an average of only 10 reports was received per year, compared with an average of 111 reports per year from 1980 to 1987, suggesting that regulatory action taken by the FDA in 1986 may have had some effect [53]. From 1996 to 1999, the FDA recalled 93 different food products that contained undeclared sulphites, and 55% of the recalled foods contained sulphites at levels that could potentially cause a severe reaction in a susceptible person.

In the early 1980s, there were also a number of reports of asthma exacerbations and/or generalized skin reactions among asthmatic patients treated with bronchodilator medications containing sulphites [45, 54–56]. One report highlighted the case of a patient who was hypersensitive to metabisulphite and developed anaphylaxis following ingestion of metabisulphite-treated food [57]. This patient had a prolonged clinical course, requiring two visits to the emergency department and 3 weeks of corticosteroid therapy, suggesting that the relapse and delayed recovery may have been related to continued exposure to sulphites during treatment. Some older, rarely used bronchodilator solutions such as isoproterenol and isoetharine contain sulphites at concentrations sufficient to cause bronchoconstriction in most asthmatic patients, even in the absence of a history of sulphite sensitivity [58]. With the availability of selective β_2-agonists such as albuterol that do not contain sulphites, these older bronchodilator solutions need not be used to treat asthmatic patients. There is also one report of sulphite-induced asthma exacerbation in a patient treated with betamethasone injections for asthma [59].

The presence of sulphites in some other pharmaceutical products is also reason for concern. There are published reports of anaphylactic or asthmatic reactions associated with the use of sulphite-containing local anaesthetics, as well as gentamicin, metoclopramide, doxycycline and vitamin B complex [11]. The generic form of the anaesthetic agent, propofol, contains sodium metabisulphite and has the potential to cause adverse effects, particularly in the paediatric population [60]. Treatment of anaphylaxis in patients who are sensitive to sulphite also poses a conundrum in that administration of adrenaline is regarded as the primary treatment for anaphylaxis, and yet all commercially available preparations of adrenaline contain metabisulphite [61]. However, even in patients with serious sulphite sensitivity, the benefit from adrenaline is considered to outweigh the risk of sulphite exposure associated with use of adrenaline in an emergency [62].

Asthmatic responses have also been reported following exposure to sulphites in occupational settings. Valero et al. [63] reported the case of a patient who experienced episodes of bronchospasm that required hospitalization after handling sodium bisulphite at work, and metabisulphite-induced occupational asthma has also been reported in a photographic technician [23] and a radiographer [64]. Occupational asthma has been reported in a worker who

sprinkled dry metabisulphite powder onto potatoes [65], and three cases of occupational asthma related to metabisulphite exposure were reported in France [66]. The use of sodium metabisulphite in the fish and prawn-processing industry, with associated exposures to high concentrations of SO_2, has been identified as an under-recognized cause of occupational airways disease [67, 68]. An increased incidence of asthma and increased asthma-related mortality have also been reported in sulphite pulp mill workers, probably as a consequence of repeated exposures to peak concentrations of SO_2 [69, 70].

Over the past three decades, a number of challenge studies have been performed, attempting to verify sulphite sensitivity and estimate its prevalence in subjects with suggestive histories. The interpretation of these studies is difficult, as the criteria for the selection of subjects have varied and may have been biased towards those with a history of sensitivity or more severe asthma. In addition, the dose and physical form of sulphite used in challenge protocols have varied widely, as have the criteria considered indicative of a positive response [1, 7, 71–73]. Questions have also been raised about the appropriateness of using changes in forced expiratory volume in 1 s (FEV_1) as an indicator of sensitivities to foods and food additives [74, 75], and it has been suggested that the sensitivity of oral metabisulphite challenge may be as low as 40% [76]. As a consequence, there is some uncertainty as to the true prevalence of sulphite sensitivity among asthmatic patients, although the literature consistently reports a prevalence of between 3% and 10% [1, 7, 12, 72, 77]. The severity of reactions also varies markedly, and they can be very severe and even life-threatening. Steroid-dependent asthmatics and those with marked AHR appear to be at greater risk of adverse reactions to sulphite-containing foods [8], but even among these 'at risk' groups ($\sim$0.5 million people in the United States [52]), reactions to sulphite vary considerably in severity. Although there was an early suggestion that as many as 30% of reported cases of sulphite sensitivity occur in individuals with no known history of asthma [78], later reviews of the literature suggested that adverse reactions to sulphites were extremely rare in non-asthmatic subjects [1, 8]. There are some indications that sulphite sensitivity may be more common among women [7, 79].

The results of some challenge studies suggest that children with chronic asthma may be particularly sensitive to sulphite, with one study reporting that 19 of 26 (66%) experienced a $>20\%$ decrease in FEV_1 following a challenge with acidic metabisulphite solutions [80]. In another study, 51 children aged 5–15 years were challenged with metabisulphite dissolved in preservative-free lemonade (to a maximum of 100 mg in 30 mL). Eighteen children (35.3%) exhibited a $>20\%$ decline in FEV_1 [81]. A similarly high percentage of positive responses was observed by Steinman et al. [82], who challenged 37 children with SO_2 in apple juice, although the percentage of positive responses decreased from 43.2% to 21.6% when a positive response was defined as a 20% rather than a 10% decline in FEV_1. Sanz et al. [83] reported a 20% prevalence of sulphite sensitivity among 20 steroid-dependent asthmatic children challenged with solutions of metabisulphite in citric acid, while another study of children with milder asthma reported the prevalences of sulphite sensitivity as 7.1% for challenges performed with metabisulphite capsules and 3.5% for challenges with sulphite solutions [84]. Among 36 children between 3 and 20 years of age with moderate asthma, a response to metabisulphite aerosol, defined as the dose causing a 20% reduction in FEV_1 (PD_{20}), was observed in 17 [85]. However, responses were more frequent among older children and there was a significant inverse correlation between age and PD_{20} metabisulphite.

Potential mechanisms of skin and respiratory sensitivities to sulphite

Given the wide variations in symptoms, in the severity of reactions and in the sensitivities of individuals to different forms of sulphite, it is unlikely that any single mechanism underlies all reactions to the sulphite additives.

Urticarial and anaphylactic reactions have been observed after exposure to local anaesthetics and parenteral products, but were not reproducible on challenge or prick testing, thereby excluding type 1 immediate hypersensitivity [11, 30]. Similarly, scratch or prick tests have rarely been positive in patients reporting urticarial reactions after dietary exposure to sulphites [86]. Positive patch test reactions in patients sensitized to sulphites indicate the potential role of delayed hypersensitivity.

A number of potential mechanisms that might explain asthmatic reactions to the sulphites have been postulated, although the mode of exposure is a confounding factor [7, 8]. Nebulized bisulphite solutions, acidified metabisulphite solutions, encapsulated metabisulphite and sulphite-containing food or drinks may or may not induce reactions in the same individual, and the types of reactions and concentrations of sulphite that induce reactions may vary widely with different forms of exposure. As mentioned previously, sulphite salts and SO_2 are in a pH-dependent equilibrium (Fig. 1), and inhalation of SO_2, generated from ingested sulphites in the warm acidic environments of the mouth and stomach, may cause respiratory symptoms. Although nebulized metabisulphite was also thought to cause bronchoconstriction through generation of SO_2 in the airways [73], airway responsiveness to acidic metabisulphite solutions and SO_2 were not significantly related [87]. Nevertheless, pH appears to be an important determinant of asthmatic responses to sulphites [88, 89], and low pH resulting in the release of high concentrations of SO_2 was suggested as

the probable cause of asthmatic responses to Spanish pickled onions [90].

Some studies have suggested that sulphites may stimulate the parasympathetic system, with bronchoconstriction being mediated by a cholinergic pathway [7]. The enzyme sulphite oxidase converts sulphite to sulphate, and it has been suggested that inadequate activity of this enzyme may result in excessive accumulation of sulphite, resulting in cholinergic-mediated bronchoconstriction in some individuals [91]. High doses of the anti-cholinergic agent, ipratropium bromide, inhibited metabisulphite-induced bronchoconstriction, although its effect varied between subjects [92]. Pretreatment with ipratropium also reduced bronchoconstriction to metabisulphite in children [85]. The PD_{20} metabisulphite after ipratropium pretreatment was inversely correlated with age, suggesting that the increase in metabisulphite responsiveness with age may reflect the increasing importance of a non-cholinergic pathway.

The release of histamine and other mediators as a consequence of mast cell degranulation through IgE- or non-IgE-mediated mechanisms has also been suggested as a possible mechanism in some individuals [93]. The mast cell-stabilizing agents, sodium cromoglycate and nedocromil sodium were potent inhibitors of bronchoconstriction when administered before a metabisulphite challenge [72, 93]. However, the histamine antagonist, terfenadine was ineffective [94], casting doubt on the role of mast cells.

Inhalation of the loop diuretic, frusemide, reduced subsequent bronchoconstriction to inhaled metabisulphite in asthmatic subjects [92]. It was possible that this effect was due to increased synthesis of prostaglandin $(PG)E_2$, which was also shown to protect against metabisulphite-induced bronchoconstriction [95]. However, another study suggested that bronchoprotective PGE_2 was unlikely to be involved in the inhibition by frusemide of airway responses to metabisulphite [96]. On the other hand, cyclooxygenase inhibitors may reduce the production of contractile PGs and thereby decrease metabisulphite-induced bronchoconstriction [97]. Leukotriene receptor antagonists also inhibited bronchoconstriction in asthmatic subjects exposed to SO_2, suggesting a possible role for leukotrienes [98, 99]. In contrast, inhalation of the nitric oxide synthase inhibitor, *N*(G)-mono-methyl-*L*-arginine (*L*-NMMA), had no effect on bronchoconstriction to metabisulphite, indicating that endogenous nitric oxide was unlikely to be involved [100].

Conclusions

Many individuals are sensitive to sulphite additives and may experience a range of symptoms, including dermatitis, urticaria, angio-oedema, abdominal pain, diarrhoea, bronchoconstriction and anaphylaxis. Nevertheless, reactions manifesting in the skin, and particularly the respiratory tract, account for the majority of cases of sulphite sensitivity. Although the literature regarding the prevalence of skin reactions to the sulphites is somewhat limited, studies suggest that somewhere between 1% and 5% of those patch tested may demonstrate skin sensitivities to these additives. Many more studies have investigated the prevalence of sulphite-induced asthma. Despite this, the true prevalence of asthmatic responses to the sulphites remains uncertain, although it is generally agreed that between 3% and 10% of adult asthmatics may show varying degrees of sensitivity to these additives, with a number of these individuals experiencing life-threatening reactions. It is important to note that the nature of the response is not determined by the manner of exposure to the sulphite additives. Thus, skin reactions may result not only from topical exposure but also following ingestion and parenteral exposure to sulphites, while topical exposure may result in respiratory symptoms in some individuals. Furthermore, skin, intestinal and respiratory reactions may occur simultaneously, and in various combinations and severities in some susceptible individuals.

The diversity of signs and symptoms associated with sulphite sensitivity makes diagnosis on the basis of clinical history very difficult. However, this is probably the only safe and practical way of identifying these sensitivities, as there are no uniformly accepted standard protocols for challenging sulphite-sensitive individuals. The lack of a standardized challenge protocol has led to some controversy in the literature regarding the prevalence of sulphite-sensitive asthma, with the dose and physical form of sulphite challenges clearly playing a role in the responsiveness of asthmatics to challenge. Another obstacle to diagnosing these sensitivities is that challenge of possible sulphite-sensitive asthmatics is potentially dangerous, especially in individuals with very severe responses.

In addition to triggering episodic and acute symptoms, sulphite additives clearly play a role in the chronic symptoms experienced by some individuals. Sensitive individuals who regularly use cosmetics or topical medications containing sulphites have been reported to exhibit chronic skin symptoms, especially on the hands, perineum and face. Similarly, occupational exposures to the sulphites have been reported to cause persistent skin symptoms. Although the possibility that exposure to sulphites may contribute to chronic asthma has not been widely explored, it is likely that unrecognized regular exposure to the sulphite additives may contribute to the chronic asthma symptoms experienced by some sensitive individuals. Sulphite additives in asthma medications may also contribute to the persistence of asthma symptoms. Reducing the exposure of sensitive asthmatics to sulphite additives may therefore lead to an improvement in asthma

symptoms, and potentially, less reliance on asthma medications.

In conclusion, the frequency of sulphite sensitivity and the extent to which these chemicals are used in foods, drinks, medicines and industry suggest that these sensitivities are clearly of clinical importance. Physicians should be aware of the range of clinical manifestations of sulphite sensitivity, as well as potential sources of exposure, including occupational settings. Despite the widespread use of these additives, identification of the offending exposure usually leads to excellent clinical outcomes after minor modifications to diet or behaviour. Alternatives that do not contain sulphite are available for most foods, drinks, medicines and cosmetics, and simple preventative measures can be undertaken to limit exposure to sulphites in occupational settings.

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