

EDITORIAL

Sulfite sensitivity

Sulfites or sulfiting agents such as the sulfur dioxide (SO_2), the salts of bisulfite (NaHSO_3 , KHSO_3) and of metabisulfite (MBS) ($\text{Na}_2\text{S}_2\text{O}_5$, $\text{K}_2\text{S}_2\text{O}_5$) are commonly used in the processing and storage of several foods and drinks. These compounds are used to inhibit both the enzymatic and non-enzymatic browning of foods and for antimicrobial and bleaching actions [1]. Several foods, including dried fruits and vegetables, wine, vinegar, potatoes, juices and pickled foods, and even some pharmaceuticals, may contain sulfites [2]. While at a neutral pH the sulfites are the main form of the sulfiting agents, at pH acid and in the presence of heat, such as in the stomach, they are transformed into bisulfite and sulfurous acid, which may be dehydrated to SO_2 , the form that might induce the bronchial adverse reactions [3].

The mechanisms of the SO_2 and MBS-induced bronchial asthma are still controversial. Even if IgE-mediated reactions have been implicated [4], the action of SO_2 on tracheobronchial receptors, inducing a cholinergic reflex, appears to be the most likely mechanism [5,6]; in fact in humans the sulfite bronchoconstriction has been attenuated by the anticholinergic agents oxitropium bromide [7,8] and ipratropium bromide [9]. However, the role of the parasympathetic system remains controversial since intravenous atropine had no effects on MBS-induced bronchoconstriction in anaesthetized guinea-pigs [10].

A possible mechanism involves a partial sulfite-oxidase enzyme deficiency: this enzyme is responsible for the final oxidation of sulfite (SO_3) to inactive sulfate (SO_4). In a recent study the possible oxidative action of vitamin B12 was able to block a sulfite-induced bronchospasm in four out of five asthmatic children [11].

A central role may be played by the kinins: in an allergic sheep model Mansour *et al.* found that the MBS-induced bronchial response was blocked by the administration of a bradykinin β_2 -receptor antagonist [12]. To support the role of the kinins in this reaction, the authors found, during the bronchial response, a ninefold increase in bronchoalveolar lavage of immunoreactive kinin levels [12]. The tachykinin depletion with capsaicin pretreatment caused a significant reduction of bronchoconstriction and airway microvascular leakage induced by MBS in guinea-pigs [13]. Furthermore, in normal volunteers the administration of an aerosolized inhibitor (Thiorphan) of neutral endopeptidase, an enzyme that cleaves and inactivates tachykinins, increases the MBS-induced airway narrowing [14].

Even if these preservatives were generally considered safe and used in the food processing, since the middle of 1970 there was an increasing concern of the possible side-effects of

their administration. The current regulations require the control of the concentrations of sulfiting agents and the label of any food containing more than 10 parts per million (ppm) of sulfites must list the preservatives as ingredients [15].

The first case report in 1976 described a non-asthmatic atopic subject with urticaria and angioedema occurring after a restaurant meal [16]. The same symptoms were noted after the oral challenge [16]. Since then there has been a large number of reports describing allergic and asthmatic reactions to sulfites. The incidence of precipitated acute bronchospasm following sulfites in food administration has been demonstrated in 5–10% adult asthmatics [17,18]; and in 35–65% children with severe asthma [19,20]. However, the prevalence of sulfite sensitivity in children is still controversial. A study by our group, evaluating the bronchoconstrictive airway responses after ingestion of varying doses of bisulfite in children with chronic asthma, showed a low prevalence of positive bronchoconstrictive reactions [21]. Furthermore, the sulfite-sensitivity was highly correlated with the methacholine reactivity [21]. Whilst in that study population, children with mild chronic asthma and stable airway conditions have been enrolled, in the original study by Towns and Mellis [20] almost all the enrolled children were in oral or inhaled steroid treatment, in other words their asthma was more severe. Therefore, the actual prevalence of sulfite sensitivity in mild to moderate asthmatic children seems to be more similar to that observed in adult patients.

In the present issue of the Journal Gastaminza *et al.* [22] presented 18 young extrinsic asthmatics with a history of asthma exacerbations few minutes after ingestion of a single pickled onion, a food that contains a high amount of SO_2 and MBS. The authors have investigated the effects of pickled onion ingestion by an oral challenge in seven of the patients, and the effect of MBS bronchial challenge test in all the study population.

The MBS challenge at pH 4.2 was positive in a 33% of the subjects; the remaining patients were tested with MBS at a lower pH (pH 3.3) and a 22% of these presented a significant drop in the lung function tests. After the ingestion of pickled onions only three out of seven patients presented a positive reaction within 3 min. None of them presented oropharyngeal symptoms like tingling pruritus or angioedema of the lips and pharynx. The absence of such symptoms reinforces the observation that sulfites and not the onion itself are responsible for the bronchoconstriction.

Interestingly, whilst all the patients presented their symptoms to pickled onion ingestion in the last 2

years, at the moment of the challenges, eight patients out of 18 did not respond to the sulfite inhalation, and four out of seven presented a lack of reaction to the pickled onion oral challenge. Even if the authors failed to demonstrate any correlation between the degree of bronchial reactivity and the challenge positivity, they hypothesized that these patients failed to respond to the challenges due to variations in the bronchial hyperresponsiveness and use of asthma-modifying treatments; most of the patients, at the moment of the challenge evaluations, were in stable condition and little medication was required; they presented clinical features similar to the population studied by our group [21].

In the diagnostic procedure of sulfite intolerance double-blind placebo-controlled tests should be performed, to assure the highest reproducibility to the challenge. However, this study has shown that several variables such as the high doses of sulfites, the pH of the food and the rough way of mastication, responsible for an extremely sudden release of SO₂, should be considered. The pH of the MBS challenge seems to play a central role in the reactivity of the patients. In fact, it is still debated even if SO₂ and MBS challenges may be considered equivalent. In a recent publication Field *et al.* found no relationship between SO₂ and MBS airway responsiveness, even if nebulized MBS is generally considered to cause bronchoconstriction via generated SO₂ [23]. Since multiple mechanisms might take place in sulfite sensitivity, differences in the response to the diagnostic challenges should be considered and probably different responses due to varying baseline condition of the disease should be observed in the same patient with sulfite intolerance.

References

- Simon RA, Stevenson DD. Adverse reactions to sulfites. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF, Yuniger JW, eds. *Allergy principles and practice*. Vol. 2, St Louis, C.V. Mosby, 1988:1557–69.
- Settipane GA. Adverse reactions to sulfites in drugs and foods. *J Am Dermatol* 1984; 10:1077.
- Fine JM, Gordon T, Sheppard D. The role of pH and ionic species in sulfur and sulfite-induced bronchoconstriction. *Am Rev Respir Dis* 1987; 136:1122–6.
- Boxer MB, Bush RK, Harris KE et al. The laboratory evaluation of IgE antibody to metabisulfites in patients skin test positive to metabisulfites. *J Allergy Clin Immunol* 1988; 82:622–6.
- Meyers DJ, Bigby, Calvayrac P et al. Interaction of cromolyn and a muscarinic antagonist in inhibiting bronchial reactivity to sulfur dioxide and to eucapnic hyperpnea alone. *Am Rev Respir Dis* 1986; 133:1154–8.
- Snashall P, Baldwin C. Mechanisms of sulphur dioxide induced bronchoconstriction in normal and asthmatic man. *Thorax*, 1982; 37:118–23.
- Dixon CMS, Ind PW. Metabisulfate induced bronchoconstriction: mechanisms. *Am Rev Respir Dis*. 1988; 137:238A.
- Dixon CMS, Ind PW. Metabisulphite induced bronchoconstriction does not involve mast cells. *Thorax* 1989; 43:226P–7P.
- Seale JP, Temple DM, Tennant CM. Bronchoconstriction by nebulized metabisulfite solutions (SO₂) and its modification by ipratropium bromide. *Ann Allergy* 1988; 61:209–13.
- Lotvall JO, Skoogh E, Lumen RJ. Bronchoconstriction induced by inhaled sodium metabisulfite in the guinea pig: effect of capsaicin pretreatment and of neutral endopeptidase inhibition. *Am Rev Respir Dis* 1990; 142:1390–5.
- Anibarro B, Caballero MT, Garcia-Ara MC et al. Asthma with sulfite intolerance in children: a blocking study with cyanocobalamin. *J Allergy Clin Immunol* 1992; 90:103–9.
- Mansour E, Ahmed A, Cortes A et al. Mechanisms of metabisulfite-induced bronchoconstriction: evidence for bradykinin B₂-receptor stimulation. *J Appl Physiol* 1992; 72:1831–7.
- Sakamoto T, Elwood W, Barnes PJ, Chung KF. Pharmacological modulation of inhaled sodium metabisulphite-induced airway microvascular leakage and bronchoconstriction in the guinea-pig. *Br J Pharmacol* 1992; 107:481–7.
- Bellofiore S, Caltagirone F, Pennisi A et al. Neutral endopeptidase inhibitor Thiorphan increases airway narrowing to inhaled sodium metabisulfite in normal subjects. *Am J Respir Crit Care Med* 1994; 150:853–6.
- Simon RA. Pulmonary reactions to sulfites in foods. *Pediatr Allergy Immunol* 1992; 3:218–21.
- Prenner B, Stevens JJ. Anaphylaxis after ingestion of sodium bisulfite. *Ann Allergy* 1976; 37:180–2.
- Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. *J Allergy Clin Immunol* 1981; 68:26–32.
- Simon RA, Green L, Stevenson DD. The incidence of metabisulfite sensitivity in an asthmatic population. *J Allergy Clin Immunol* 1982; 69:118A.
- Friedman ME, Easton JG. Prevalence of positive metabisulfite challenges in children with asthma. *Ped Asthma Allergy Immunol* 1987; 1:53.
- Towns SJ, Mellis CM. The role of acetylsalicylic acid and sodium bisulfite in chronic childhood asthma. *Pediatrics* 1984; 73:631–7.
- Boner AL, Guarise A, Vallone G et al. Metabisulfite oral challenge: incidence of adverse responses in chronic childhood asthma and its relationship with bronchial hyperreactivity. *J Allergy Clin Immunol* 1990; 85:479–83.
- Gastaminza G, Quince S, Torres M et al. Pickled onion-induced asthma: a model of sulfite-sensitive asthma? *Clin Exp Allergy* 1995; 25.
- Field PI, McClean M, Simmul R, Berend N. Comparison of sulphur dioxide and metabisulphite airway reactivity in subjects with asthma. *Thorax* 1994; 49:250–6.

D. G. PERONI

A. L. BONER

*Clinica Pediatrica-Università di Verona,
Policlinico Borgo Roma,
37134 Verona, Italy*

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.