

Asthma and Food Additives

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KEY CONCEPTS

- Food additives are an uncommon cause of asthma exacerbations.
- Sulfiting agents can provoke acute and occasionally severe episodes of bronchoconstriction.
- Monosodium glutamate is unlikely to provoke bronchoconstriction.
- Tartrazine has not been definitely shown to cause airflow obstruction.
- A definite diagnosis of food-additive-induced asthma requires properly performed challenges.

Introduction

Food additives are substances added to food products for a wide variety of functions, including coloring, flavoring, nutrient, and antimicrobial purposes. Because additives are typically minor ingredients in food, the intake of additives is usually small. An estimated 23–67% of asthmatics perceive that food additives exacerbate their asthma. However, the prevalence rate of food-additive-induced asthma exacerbations obtained by double-blind, placebo-controlled trials is less than 5%. Because the current therapy for food-additive-induced asthma is avoidance or elimination of inciting agents, a correct diagnosis is imperative to avoid unnecessary dietary restriction. Sulfites, monosodium glutamate (MSG), and tartrazine will be discussed in detail in this chapter.

Evaluating asthma studies

A variety of data are available implicating sulfites, MSG, and tartrazine in asthma exacerbations, but many of the studies are of poor design.

Well-designed studies in asthmatic subjects require stable lung function at baseline. When the subjects have wide variability in peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV1) at baseline, variability seen during the challenge may be related to the substance or a reflection of poor asthma control. If asthma medications are discontinued, the timing in relation to the challenge must be carefully evaluated. For example, anti-asthmatic and

anti-allergic medications that can inhibit a response must be withheld before a challenge. β_2 -agonists are typically withheld the day of the challenge, and cromolyn sodium or antihistamines are withheld 24 hours prior to the challenge. Asthma controller medications such as theophylline and inhaled or oral corticosteroids may be continued, since they do not interfere with the response.

If rescue medications are given within 3 hours of a challenge, lung function declines 6 hours after challenge, the decline is more likely due to a waning of medication effect rather than bronchoconstriction from the challenge substance. Consistent timing of challenges is important to exclude confounding due to the physiologic diurnal variability in PEFR. To eliminate observer bias, challenges should be double-blinded and placebo-controlled.

The method of administration of challenge substance may influence results. For example, some asthmatics respond to oral capsule challenges, while others respond only to challenge with solutions (e.g. sulfites). The route of administration chosen in diagnostic challenges should be tailored to the patient's history.

The reliability of the pulmonary function measure used is another key aspect. The flow-volume loop obtained with spirometry is precise and reproducible, while PEFR is more variable. Criteria used to define positive challenges should be considered.

Duration of subject evaluation following a challenge is also important. For MSG, subjects are evaluated for as few as 2 or as many as 14 hours following challenge. Determining when reactions are most likely to occur and still be linked to the challenge substance will help determine the length of time subjects should be observed.

For sulfites, MSG, and tartrazine, various data are presented and evaluated using the criteria outlined above.

Sulfites

Sulfiting agents have been used in foods for many years. Although sulfites are often added to foods, they occur naturally in certain foods such as mushrooms and Parmesan cheese.

Adding sulfites to foods serves many purposes, for example, inhibition of enzymatic and non-enzymatic browning, antimicrobial actions, bleaching, and as a dough conditioner. Sulfites are also used in pharmaceutical agents, including medications for the treatment of allergic diseases and asthma.

Common forms of sulfites used as food or drug additives include sulfur dioxide (SO_2), inorganic sulfite salts, sodium or potassium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$ or $\text{K}_2\text{S}_2\text{O}_5$), sodium or potassium bisulfite (NaHSO_3 or KHSO_3), and sodium or potassium sulfite ($\text{Na}_2\text{S}_2\text{O}_3$ or $\text{K}_2\text{S}_2\text{O}_3$). Sulfites can react with a variety of food constituents. Dissociable forms of sulfite can serve as reservoirs of “free” sulfites. Irreversibly bound sulfites are removed permanently from the pool of sulfites that may exist in foods.

The form of sulfite present in foods is affected by pH. For example, a low-pH favors H_2SO_3 , intermediate pH (4.0) favors HSO_3^- , and high-pH favors SO_3^{2-} . In solution, especially at an acid pH (saliva, gastric juice) and in the presence of heat (stomach), sulfites are readily transformed into bisulfite and sulfurous acid. These substances may then be volatilized to SO_2 , which has been implicated in causing bronchoconstriction.

The estimated prevalence of sulfite sensitivity in adult asthmatics is approximately 5%, with a higher prevalence in moderate to severe persistent asthmatics. Two hundred and three patients initially underwent a single-blind challenge with sulfite-containing capsules. If the single-blind challenge were positive (20% or greater decrease in FEV1 from baseline), a double-blind challenge followed. In the single-blind challenge, 16 of 83 moderate to severe persistent asthmatics had a positive response, while only 5 of 120 less severe asthmatics had a positive response. When these results were confirmed with double-blind challenges, three of seven more severe asthmatics and one of five less severe asthmatics had a positive response. The estimated prevalence of sulfite sensitivity in non-steroid-dependent asthmatics based on the double-blind challenge results was 0.8%. In the more severe asthmatics, the prevalence was higher (8.4%). The estimated prevalence of sulfite sensitivity in the asthmatic population as a whole is less than 3.9% and those with moderate to severe persistent asthma are at most risk.

The largest group of sulfite-sensitive asthmatics are individuals who respond to ingestion of acidic sulfite solutions. Among these patients, some react to acidic sulfite solution challenge and others do not, a phenomenon perhaps explained by variable inhalation of SO_2 .

The mechanism by which sulfites induce asthma symptoms has not yet been fully elucidated. Various hypotheses have been proposed to explain the bronchoconstriction by SO_2 : a cholinergic reflex mechanism, an IgE-mediated mechanism, or deficiency of sulfite oxidase. The cholinergic reflex mechanism suggests that inhaled SO_2 , such might occur when swallowing an acidic sulfited beverage, acts on irritant receptors in the lung. This hypothesis is supported by the fact that the response in sulfite-sensitive individuals can be blocked by the administration of anticholinergic drugs, such as inhaled atropine or doxepin, an antihistamine with anticholinergic properties.

Another proposed mechanism is an IgE-mediated mechanism. This mechanism has not yet been proven, but is supported by the presence of positive skin prick tests to sulfites and by anaphylaxis in certain individuals.

Sulfite oxidase deficiency has also been proposed as an explanation. Sulfite oxidase metabolizes sulfite (SO_3) to inactive sulfate (SO_4), and a decrease in sulfite oxidase activity has been seen in skin fibroblasts of sulfite-sensitive asthmatics compared with controls [1].

Although sulfite-induced asthma is typically triggered by the ingestion of a sulfited food, beverage, or drug, inhalation of SO_2 can also be a trigger. Several factors determine the likelihood of an adverse reaction: the nature of the food, the level and form of residual sulfite in the food, and the sensitivity of the patient. Sulfite-sensitive asthmatics are most likely to respond to “free” sulfites. However, the degree of sensitivity these patients have to the various forms of sulfites in foods has yet to be elucidated.

The levels of sulfiting agents in foods are usually expressed as SO_2 equivalents because sulfite salts can release SO_2 under some assay conditions. In the United States, total daily *per capita* intake of sulfites in foods is approximately 6-mg SO_2 . The threshold response to challenges with sulfites in sensitive asthmatics is typically between 12- and 30-mg SO_2 equivalents (20 to 50-mg potassium metabisulfite).

The levels of sulfites in foods vary (see Chapter 29) and are typically expressed as parts per million (ppm). One part per million equals one microgram per gram. The highest levels (up to 1000 ppm) are contained in dried fruits and lemon, lime, grape, and sauerkraut juices. Food processing and preparation may decrease sulfite levels. Therefore, the amounts of sulfite used initially to treat foods will not necessarily reflect residue levels after processing, storage, and preparation. Food processing also differs in various countries, so caution must be used in interpreting reports from other countries that implicate sulfites in eliciting asthma symptoms.

Inhaling as little as 1 ppm SO_2 has been demonstrated to cause bronchoconstriction in asthmatics. In doses of 1–50 ppm, 99% of inhaled SO_2 is absorbed by the upper airway. The resulting bronchospasm may be initiated by stimulation of superficial afferent nerve endings in the larynx

or tracheobronchial tree and then mediated by parasympathetic pathways in the bronchi.

Although the precise mechanism has yet to be elucidated, the bronchoconstriction caused by exposure to sulfites in sensitive asthmatics can be severe and potentially life threatening. Therefore, accurate diagnosis is imperative. But because history does not always correlate with a positive challenge, history alone is insufficient for the diagnosis of sulfite-induced asthma. Skin prick tests and serologic tests are also not reliable in the diagnosis of sulfite-induced asthma. The diagnostic tool with the highest reproducibility is a double-blind, placebo-controlled challenge. However, there is no standardized procedure for challenging with sulfiting agents (see Tables 29.1 and 29.2 for suggested protocols for sulfite challenges). Patients may be challenged with capsules, neutral solutions, or acidic solutions of metabisulfite. A capsule challenge may be preferred, as most exposures are to sulfites in bound form in foods rather than to sulfites in free form, such as in lettuce. Variable thresholds for bronchospastic responses have been seen, from 5 to 200 mg of encapsulated metabisulfite. A challenge with sulfites in solution is optimal for patients who have reacted to beverages such as sulfited wines. In patients with a history of response to particular foods, food challenges are used diagnostically. Challenges, therefore, can be tailored to a patient's history of reaction.

Challenges should be conducted very carefully, with availability of equipment necessary to treat severe bronchospastic or anaphylactic reactions. Because certain drugs can inhibit the response to sulfites, anti-asthmatic and anti-allergic medications, such as β_2 -agonists, cromolyn, and antihistamines, should be withheld before challenges. β_2 -agonists are typically withheld the day of the challenge, while cromolyn and antihistamines are withheld at least 24 hours prior to the challenge. Theophylline and corticosteroids (inhaled and oral) can be continued, for these drugs do not interfere with sulfite-induced reactions.

Typically, if a single-blind challenge is positive, the results should be confirmed with a double-blind challenge. Randomization of administration of active and placebo challenges should be done, possibly with a third challenge day, to avoid an order effect of challenge. An order effect of challenge has been seen in patients who receive placebo on the first day and do not react but do react on subsequent challenge days regardless of whether they receive placebo or active challenge.

Given the diagnosis of sulfite-induced asthma with an appropriately performed challenge study and the establishment of a threshold dose of sulfite that provokes asthma, treatment is strict avoidance of sulfite-treated foods and drugs, especially those containing greater than 100-ppm SO_2 equivalents. In the United States federal regulations requires foods and alcoholic beverages containing greater than 10-ppm total SO_2 , be labeled. Unlabeled sulfited foods

still exist in restaurants, although the use of sulfites in fresh foods such as fruits and vegetables in salad bars has been banned. Residue levels of sulfites in shrimp, which are used to prevent enzymatic browning (black spot formation), are still permitted. Imported table grapes are treated with sulfites to inhibit mold growth, but they must be detained at their port of entry until sulfite residues are no longer detected. Potatoes can be sulfited, so patients with sulfite-sensitive asthma should avoid all potatoes in restaurants, except those baked with intact skins. Sulfite-sensitive asthmatics should avoid sulfite-containing pharmaceutical agents such as certain bronchodilator solutions, subcutaneous lidocaine, and intravenous corticosteroids. Pharmaceutical corporations have eliminated the use of sulfites in many products used for the treatment of asthmatics, although epinephrine contains sulfites as antioxidants because there is no alternative agent. The positive effects of the epinephrine overwhelmingly negate any negative effects of sulfites. Epinephrine therefore should *never* be withheld from sulfite-sensitive asthmatics when indicated.

Complete avoidance of sulfites is difficult, and reactions can be severe. Management of reactions includes administration of β_2 -agonist medications or nebulized atropine and self-administered epinephrine for severe episodes of sulfite-induced asthma.

Monosodium glutamate

Just as sulfites have been linked to asthma exacerbations in some asthmatics, MSG has also been implicated. Unlike sulfites, however, there is little data to confirm that MSG causes bronchospasm.

MSG is a sodium salt of the non-essential amino acid, L-glutamic acid. MSG occurs naturally in a wide variety of foods. MSG exists in free form and bound to proteins and is used as a flavor enhancer in processed foods. In the United States, the average daily intake of MSG is 0.2–0.5 g. As much as 4–6 g might be ingested in a highly seasoned restaurant meal.

Because MSG is perceived as a food chemical likely to cause bronchoconstriction, it is a frequently avoided food item. However, the role of MSG in exacerbating asthma has not been firmly established. Levels of MSG precipitating adverse events are much higher than the usual dietary exposure (2.5–3 g versus 0.2–0.5 g daily exposure) and occur in the absence of food.

Thirty-two asthmatic patients with a history of MSG-induced asthmatic reactions were evaluated via single-blind, placebo-controlled oral challenge with MSG. PEFR were followed hourly for 14 hours after oral challenge. Thirteen exhibited significant declines in PEFR. Patients were given placebo on day 1 of the study and then challenged with MSG on days 2 and 3, augmenting the lack of daily controller medications, which were stopped just prior to commencement

of the study. Some patients were allowed to have rescue medication within 3 hours of initial challenge, therefore declines in PEF_R 6 hours or more after challenge were most likely due to waning effects of β_2 -agonist rather than to bronchoconstrictive effects of MSG. The results of this study were not reproduced; a non-blinded challenge was repeated in only one patient.

Oral challenges with 1.5g of MSG in 12 asthmatic patients found no changes in FEV₁ that was statistically different from placebo. The number of patients evaluated was small, and subjects were only evaluated for 2 hours after challenge, rather than 12 hours or more as in other studies. This study does suggest that in the usual quantities found in food, MSG is unlikely to induce bronchoconstriction.

Another study evaluated 12 asthmatics, all of whom had a history of asthma exacerbation with MSG ingestion. This was a double-blind, placebo-controlled study to evaluate for MSG-induced bronchial hyperresponsiveness. Methacholine challenge was performed before and after oral challenge with MSG. The results of this study were completely negative. This study involved a small number of subjects, and patients were directly monitored for only 4 hours after challenge. Nevertheless, MSG-induced asthma was not demonstrated in this group of adult asthmatics with prior history of asthma symptoms precipitated by MSG.

A single-blind, placebo-controlled study evaluated 100 asthmatic patients, 30 of whom reported prior asthma exacerbations with MSG exposure. Subjects were given 2.5g of MSG, and FEV₁ was measured at hourly intervals for 12 hours. No significant drop in FEV₁ occurred, and no patients developed asthma symptoms.

In contrast to the general perception that MSG-induced asthma exists, well-designed studies with oral challenges of MSG clearly have not demonstrated changes in FEV₁ or symptoms of asthma. Currently, there is limited evidence that patients with asthma are more at risk for adverse effects from MSG than the general population [2].

When patients are concerned that a reaction may be occurring to MSG, an oral challenge can be performed (Table 27.1). Maintenance asthma medications should be continued. An initial single-blind, placebo-controlled challenge should be done. FEV₁ should be monitored hourly after each of five doses of placebo. If the FEV₁ changes by more than 10%, the patient has failed the placebo challenge. If the FEV₁ is stable (change of less than 10%), a second placebo challenge should be performed and FEV₁ monitored hourly for up to 12 hours.

If patients “pass” the placebo challenge day with less than 10% variability in FEV₁, a single-blind challenge with MSG should be performed. MSG is given in five 500mg capsules, totaling 2.5g. FEV₁ is monitored hourly for a total of 12 hours. Five placebo capsules should be given at the 6-hour point to maintain a sequence similar to the placebo challenge day. A positive response is defined as a drop in FEV₁

Table 27.1 Protocol for MSG Oral Challenge

<i>Single-blind challenge</i>
Continue maintenance asthma medications
Perform on initial single-blind placebo challenge
• Administer five placebo capsules of 500-mg sucrose each • Monitor FEV₁ hourly • Failure of placebo challenge is a change in FEV₁ > 10% • If FEV₁ remains stable, perform a second placebo challenge, monitoring FEV₁ hourly • Total duration of placebo day: 12 hours
If patients pass the placebo challenge day, perform single-blind challenge with MSG
• Give five capsules MSG totaling 2.5 g • Monitor FEV₁ hourly for total of 12 hours • Six hours after MSG administered, administer five placebo capsules to maintain a sequence similar to the placebo challenge day • Positive response is FEV₁ drop > 20% (perform double-blind challenge to confirm)
<i>Double-blind challenge</i>
• Continue maintenance asthma medications • Repeat 12-hour placebo challenge on 1 day • Request repeat MSG challenge as above on another day • Challenge day (placebo or active) should be in random order.

of greater than 20%. If patients have a positive response to a single-blind challenge, a double-blind challenge should be performed.

Tartrazine

Synthetic colorants are often added to foods. One such example is the azo dye, tartrazine, also known as FD&C Yellow #5. As with MSG, many of the reported studies have design flaws. No well-designed study has corroborated claims that tartrazine provokes asthma exacerbations, for example, lack of baseline asthma stability, withholding of asthma medications, or proper controls.

In 194 aspirin-sensitive patients evaluated for tartrazine sensitivity by oral challenge, no cross-sensitivity between aspirin and tartrazine was demonstrated. The authors conclude that reports of tartrazine-induced bronchospasm represent spontaneous asthma coincidentally associated with ingestion of tartrazine, rather than bronchospasm caused by tartrazine. None of the subjects had positive reactions when double-blind, placebo-controlled challenges were performed [3].

If a patient is concerned about reactions to tartrazine, an oral challenge can be performed (Table 27.2). An initial challenge should involve hourly FEV₁ monitoring throughout the challenge. Placebo should be administered first. If FEV₁ remains stable after 3 hours, 25-mg tartrazine can be given. If after another 3 hours, FEV₁ is still stable, 50-mg tartrazine can be administered. A “conditionally positive”

Table 27.2 Protocol for tartrazine oral challenge*Initial challenge*

Administer placebo first

Monitor FEV1 hourly

If FEV1 stable after 3 hours, administer 25-mg tartrazine

If FEV1 stable after 3 hours, administer 50-mg tartrazine

A "conditionally positive" test consists of FEV1 drop of 25% or more after the 25- or 50-mg dose tartrazine

Double-blind challenge

Begin with a full day of placebo challenge using three doses of placebo administered 3 hours apart

Monitor FEV1 hourly

On the following day, follow protocol for initial challenge using suspected provoking dose of tartrazine and two placebos

test consists of an FEV1 drop of 25% or more after the 25- or 50-mg dose of tartrazine.

When the initial challenge is positive, a double-blind challenge should be done, using the suspected provoking dose of tartrazine and two placebos. This double-blind challenge should be preceded by a full day of challenge using three doses of placebo administered 3 hours apart. FEV1 should be monitored hourly throughout the placebo challenge and active challenge.

Conclusions

Despite that a multitude of food additives exist, only a few are commonly implicated in asthma: sulfites, MSG, and tartrazine. Of these three, only sulfites have been found to incite bronchoconstriction in some asthmatics, who should avoid sulfite exposure. In contrast, due to the lack of evidence in well-designed studies linking MSG and tartrazine to asthma exacerbation, asthmatic patients need not avoid exposure to MSG or tartrazine if a double-blind, placebo-controlled challenge is negative.

References

- 1 Simon RA. Update on sulfite sensitivity. *Allergy* 1998;53:78–9.
- 2 Geha RS, Beiser A, Ren C, *et al.* Review of alleged reaction to monosodium glutamate and outcome of a multicenter double-blind placebo-controlled study. *J Nutr* 2000;130:1058S–62.
- 3 Stevenson DD, Simon RA, Lumry WR, Mathison DA. Pulmonary reactions to tartrazine. *Pediatr Allergy Immunol* 1992;3:222–7.