Asthma and Anaphylactoid Reactions to Food Additives

SUSAN M. TARLO, MB, BS, FRCPC
GORDON L. SUSSMAN, MD, FRCPC

Numerous agents are added to the food we eat: colouring agents, preservatives, antioxidants, flavouring agents, stabilizers, thickeners, and so on. Only a few of these agents are currently known to play a role in precipitating allergiclike reactions (typically urticaria, angioedema, asthma, and anaphylaxis).

The mechanism of the reaction caused by the best-studied ingested food additives (sulfites, monosodium glutamate, tartrazine, and benzoates) remains unknown, although certain agents, such as gums, can clearly cause a typical immunoglobulin E (IgE)-mediated allergic response. This article discusses the clinical features, diagnosis, and management of asthma, urticaria, and anaphylactic responses caused by common food additives (Table 1).

Dr Tarlo is Head of an Allergy Clinic and Occupational Lung Disease Clinic at the Western Division of the Toronto Hospital and is a Research Physician at the Gage Research Institute in Toronto. Dr Sussman is Head of the Section of Allergy, Division of Immunology, at Wellesley Hospital and is an Assistant Professor at the University of Toronto.

Sulfites
Sulfiting agents are used mainly as antioxidants in food fresheners and to control microbial growth in fermented beverages (Table 2). Studies have suggested that 5% to 10% of asthmatic patients experience an exacerbation of their asthma within 10 to 20 minutes of ingesting sulfites.1-4 Severity of reaction ranges from mild symptoms after ingesting a large amount to life-threatening responses after ingesting small amounts.5,6 The response most commonly manifests as asthma alone but can include flushing, urticaria, angioedema, tearing, runny nose, abdominal pain, seizures, and anaphylaxis.1,4,7,8 Extremely sensitive patients have died from such responses.1-4

Sulfites in foods or drinks can be present as sulfur dioxide, sodium sulfite, sodium or potassium metabisulfite, and sodium or potassium bisulfite. Sulfites were commonly used in restaurants to keep salads and uncooked vegetables looking crisp and fresh. However, after one sulfite-related death in Canada, this use was banned. Sulfites can still be used as a whitener for potatoes, grapes, and shrimp. Legislation requiring the nature and concentration of sulfite to be labeled is expected. Today, the most common sources of

SUMMARY
Presumed allergic reactions to hidden food additives are both controversial and important. Clinical manifestations include asthma, urticaria, angioedema, and anaphylactic-anaphylactoid events. Most adverse reactions are caused by just a few additives, such as sulfites and monosodium glutamate. Diagnosis is suspected from the history and confirmed by specific challenge. The treatment is specific avoidance.

RÉSUMÉ
Les présomées réactions allergiques aux additifs alimentaires font l'objet de controverses mais sont importantes. Parmi les manifestations cliniques, on note l'asthme, l'urticaire, l'angioedème et les incidents anaphylactiques-anaphylactoïdes. La plupart des réactions indésirables sont causées par un petit nombre d'additifs, tels les sulfites et le glutamate monosodique. On peut soupçonner ce diagnostic à l'histoire et le confirmer par des tests de provocation spécifiques. Le traitement consiste à éviter l'agent causal.

Table 1. Common food additives known to cause adverse reactions

<table>
<thead>
<tr>
<th>ADDITIVE</th>
<th>REACTION</th>
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<tbody>
<tr>
<td>Sulfites</td>
<td>Asthmatic attack</td>
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<td></td>
<td>Anaphylaxis</td>
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<td></td>
<td>Abdominal pain</td>
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<td></td>
<td>Urticaria and angioedema</td>
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<td>Rhinoconjunctivitis</td>
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<td></td>
<td>Seizure</td>
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<td></td>
<td>Death</td>
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<td>Monosodium glutamate</td>
<td>Chinese restaurant syndrome</td>
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<tr>
<td>Butylated hydroxytoluene</td>
<td>Late and immediate onset asthma</td>
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<td>Butylated hydroxyanisole</td>
<td>Chronic urticaria</td>
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<tr>
<td>Tartrazine</td>
<td>Asthma</td>
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<tr>
<td>Nitrites, nitrates</td>
<td>Gastrointestinal complaints</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Urticaria and angioedema</td>
</tr>
</tbody>
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Adapted from Tang.

Sulfites are beer, wine, dried apricots, other dried fruit, frozen French fries, frozen seafood, jams, jellies, and bottled fruit juices.

The mechanism of the asthmatic response to sulfites is unknown. A few sulfite-sensitive patients have positive skin reactions to sulfites, indicating an IgE-mediated allergic reaction. Another proposed mechanism is a local response to released sulfur dioxide or sulfite inhalation, as asthmatics have been shown to be particularly responsive to the irritant bronchoconstrictor effect of inhaled sulfur dioxide. However, studies have indicated no clear relationship between inhaled sulfur dioxide, airway responsiveness, and ingested sulfite sensitivity, suggesting that other factors also play a role in the response. Sulfite oxidase deficiency has been identified by fibroblast tissue cultures in sulfite-sensitive patients. Such a deficiency could delay clearance of a sulfite load and magnify the effect of sulfites.

Some multidose bronchodilator solutions for aerosolization previously contained sulfites as preservatives but no longer do. Freon-propelled inhalers do not contain sulfites. Some injectable solutions, such as epinephrine, do contain sulfites as preservatives, but the amount injected has not been shown to precipitate asthma or anaphylactoid responses.

Sulfite sensitivity should be suspected if a patient's history indicates asthma exacerbation within 20 minutes of ingesting foods or beverages. If a definitive diagnosis is necessary, single- or double-blind challenge testing can be carried out. This carries some risk and is contraindicated in patients with a history of very severe response. It should be performed only in a hospital with staff and facilities for resuscitation in the event of a severe reaction, and with the patient's informed consent. As with any challenge of food additives (Table 3), a control day with placebo challenge is required (using lactose or, if the patient is lactose intolerant, xylose). The patient should avoid sulfite-containing foods for at least 5 days before challenge.

The challenge should consist of repeated increasing doses of potassium metabisulfite administered at intervals depending on the timing of symptoms recorded in the history (generally every 20 minutes). Powdered metabisulfite or placebo is dissolved in 10 mL of water or juice, and the patient is asked to hold the solution in his or her mouth for 30 seconds before swallowing it. Increasing doses of metabisulfite (eg, 1 mg, 5 mg, 15 mg, 45 mg, 100 mg, or smaller increments in those with severe symptoms) are used for challenge, and the response is monitored by spirometry before, and 20 minutes after, each dose. If the forced expiratory volume in 1 second, or $FEV_1$, falls 20% or more, the challenge is stopped for the day, and the patient is monitored until clinically improved. An $FEV_1$ that falls as much as, or more than, 20% more than on the placebo day indicates a positive response to sulfites. Medication use should be consistent both days; guidelines for discontinuing medications should be followed as in other challenges (Table 3).

Treatment is by avoidance and patient education on the appropriate management of symptoms caused by inadvertent
Monosodium glutamate

Monosodium glutamate (MSG) is added to food to enhance flavour. It is present most frequently in Chinese restaurant food and is also in commercially prepared soups, stews, and other main dishes in quantities of up to 5 g per portion.

The most common manifestation of MSG sensitivity (Chinese restaurant syndrome) occurs 1 to 2 hours after MSG ingestion and is characterized by headache, nausea, sweating, chest tightness, burning, and numbness. Occasionally, severe symptoms mimic angina. Asthma exacerbations have been documented rarely but can occur up to 12 hours after MSG ingestion. Sensitivity to MSG appears to be far less common clinically than sulfite sensitivity. The mechanism is unknown, but the symptoms could be caused by stimulation of irritant receptors in the airways or by a central effect.

If the diagnosis is suspected from the history, a trial of MSG avoidance and specific oral challenge testing can be done. Either MSG (in doses ranging from 500 mg to 3 g) or lactose placebo are given by capsule. The challenge procedure is similar to that for sulfites with a placebo control day, patient blinding, and consent. However, the follow-up time after each dose could be several hours, depending on the timing of previous presumed reaction to MSG noted in the history.

Tartrazine and benzoates

Tartrazine is a yellow dye used in some yellow, orange, and green colours for foods, drinks, and medications. Benzoates are used as preservatives in jams, jellies, pickles, and soft drinks. Studies have reported that these additives exacerbate asthma, urticaria, and angioedema, particularly in acetylsalicylic acid–sensitive asthmatics (8% to 44% in some studies). However, studies during the past 12 years with double-blind challenge testing have shown only rare patients to be truly sensitive to these agents. Thus, an avoidance diet is unjustified for ASA-sensitive asthmatics unless carefully compared with a normal diet by peak flows, symptom scores, and medication requirements. Apparent improvements with avoidance should be documented by single- or double-blind challenges as described for the other additives before placing patients on long-term, very restrictive diets.

The mechanism of the response is unknown, but tartrazine and benzoate have been reported to stimulate lymphocyte-derived and leukocyte inhibitory factors, suggesting a possible role for cell-mediated immunity.

Other ingested food additives

Other food additives, such as spices and gums, can cause IgE-mediated events as in true food allergy (urticaria, angioedema, asthma, or anaphylaxis). When an allergy history suggests reactions to foods containing such agents, skin testing and, where needed, single- or double-blind oral challenges can be helpful.

Aspartame has been reported to precipitate urticaria in a few patients, but to date this has not been proved by double-blind challenge.

Antimicrobial drugs

Health and Welfare Canada has limited the allowable levels of almost all antibiotics found in milk, poultry, and meat. Although these levels are extremely low (0.01 to 4 ppm maximum residue), they could be responsible for IgE-mediated allergic reactions in susceptible individuals. Patients with suggestive histories should undergo appropriate investigations (skin tests or challenge).

Inhaled food additives

In addition to ingested food additives, inhaled food additives, especially among food-industry workers, can cause or exacerbate rhinitis, conjunctivitis, and asthma. Examples include enzymes, such as fungal amylase used by bakers and in flour manufacture; papain used as a meat tenderizer; sulfites used to make frozen french fries; and pectin used in jam production. Patients who inhale food additives at work may have a history of exacerbation of symptoms during the week with improvement on weekends and holidays. Investigations should include documentation of a work relationship by serial

Table 2. Common sources of food additives

| SULFITES | • Wine  
| | • Beer  
| | • Salad bars  
| | • Frozen french fries  
| | • Dried fruit, eg, apricots, white raisins  
| | • Lemon concentrates for cooking or drinks  
| | • Some baked goods  
| MONOSODIUM GLUTAMATE | • Chinese meals  
| | • Soups  
| | • Stews  
| TARTRAZINE | • Jams  
| | • Some butter  
| | • Candies  
| | • Cakes  
| | • Tablets  
| BENZOATES | • Some soft drinks  
| | • Pickles  
| | • Jams  
| | • Jellies  
| | • Cakes  

Canadian Family Physician VOL 39 May 1993 1121
peak flow recordings and repeat measurements of airway responsiveness at work and off work; skin testing where feasible (eg, with inactivated papain); and, if needed, specific inhalation challenge in a specialized unit. Treatment, after establishing the diagnosis, is again by avoidance.

Conclusion

Food additives should be considered as possible triggering factors among patients with asthma, urticaria, angioedema, or anaphylaxis. During history-taking all patients should be asked whether meals or drinks appear to precipitate symptoms. If symptoms appear to be provoked by several different foods or drinks, the possibility of a common food additive should be considered and further investigated. A trial of additive avoidance can be used, but it should be carefully monitored and compared with symptoms during a similar period on a normal diet. Blinded challenges can also be helpful. Inhaled food additives should be considered among food workers with symptoms of allergy suggestive of occupational exposure.

Requests for reprints to: Dr S.M. Tarlo, Toronto Hospital (Western Division), Edith Cavell Wing, #4008, 399 Bathurst St, Toronto, ON M5T 2S8

References

ADVERSE REACTIONS: Gastrointestinal: In subjects receiving CYTOTECH (misoprostol) 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain and flatulence. The average incidences of these events were 11.4%, 6.8% and 2.5%, respectively, in clinical trials using a dosage regimen of 400 mcg bid, the incidence of diarrhea was 12.8%. The events were usually transient and mild to moderate in severity. Diarrhea, when it occurred, usually developed early in the course of therapy, was self-limiting and required discontinuation of CYTOTECH in less than 2% of the patients. The incidence of diarrhea can be minimized by adjusting the dose of CYTOTECH by administering after food, and by avoiding co-administration of CYTOTECH with magnesium-containing antacids. Gynecologic: Women who received CYTOTECH during clinical trials reported the following gynecological disorders: spotting (6.8%), cramps (0.6%), menorrhagia (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Epigastric: There were no significant differences in the safety profile of CYTOTECH in 500 ulcer patients who were 65 years of age or older, compared with younger patients. Confusion has been reported in a small number of patients in our post-marketing surveillance of CYTOTECH. Incidence greater than 5%: In clinical trials, the following adverse reactions were reported by more than 1% of patients: epigastric distress, dyspepsia, abdominal pain, burning abdominal pain, nausea and vomiting. No significant differences in the incidence of these events for CYTOTECH and placebo.

DOSEAGE AND ADMINISTRATION: Treatment and Prevention of NSAID-induced Gastric Ulcer: The recommended adult oral dosage of CYTOTECH (misoprostol) for the prevention and treatment of NSAID-induced gastric ulcer is 400 to 800 mcg a day, divided doses. NSAIDs should be taken according to the schedule prescribed by the physician. When appropriate, CYTOTECH and NSAIDs are to be taken simultaneously. CYTOTECH should be taken after food. **Duodenal Ulcer:** The recommended adult oral dosage of CYTOTECH (misoprostol) for duodenal ulcer is 800 mcg per day for 2 weeks or 4 weeks divided doses (i.e., 200 mcg qid or 400 mcg bid). The last dose should be taken at bedtime with food. Antacids (aluminum based) may be used as needed for relief of pain. Treatment should be continued for a total of 4 weeks unless healing in less than 4 weeks has been documented by endoscopic examination. In the small number of patients who may have fully healed after 4 weeks, therapy with CYTOTECH may be continued for a further 4 weeks. Use in Safety and Renally Impaired: Consideration for Dose Adjustment (See Doseage And Administration). Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of T1/2, Cmax and AUC compared to normals. There was no clear correlation between degree of impairment and AUC. In subjects over 64 years old the pharmacokinetics may be affected. In both patient groups the pharmacokinetic changes are not clinically significant. No routine dosage adjustment is recommended in older patients or those patients with renal impairment. Dose adjustment may need to be reduced if the usual dose is not tolerated. In patients with renal failure, a starting dose in the low range (100 mcg qid) is recommended. Drug Interactions: The serum protein binding of misoprostol (the active metabolite of misoprostol) was not affected by: indomethacin, ranitidine, digoxin, phenytoin, warfarin, diazepam, methylprednisolone, theophylline, cyclosporine, and cyclophosphamide (mean serum levels). Lowered protein binding of misoprostol from 84% to 52%, was not been clinically significant since the binding of misoprostol is not essential for elimination. The elimination half-life (t1/2) is very short. In summary, misoprostol has no significant affect on the cytochrome P450 - linked hepatic mixed function oxidase system and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system. No drug interactions attributable to misoprostol have been observed to date. (See CLINICAL PHARMACOLOGY). Some pharmacists and specialists in pharmacology have the capacity to produce hypotension through peripheral vasodilation. The results of clinical trials to date indicate that CYTOTECH has not produced hypotension at dosages effective in promoting the healing of ulcers. Nevertheless, CYTOTECH should be used with caution in the presence of disease states where hypertension might precipitate serious cardiovascular or cerebrovascular disease, acute coronary artery disease or chronic arterial disease. Episodic asthesiae have been reported with prostaglandins and prostaglandin analogues administered by routes other than oral. Therefore, misoprostol tablets should be used in known epileptics only when their epilepsy is adequately controlled and then only when expected benefits outweigh potential risks. Symptomatic responses to CYTOTECH do not preclude the presence of gastric malignancy.