Gastroenterology and Hepatology From Bed to Bench

EDITORIAL

Considerations for the diagnosis and management of sulphite sensitivity

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The review article by Vally and Misso (1) published in the current edition of this journal outlines the broad range of signs and symptoms associated with sulphite sensitivity. These include bronchoconstriction, wheezing, dyspnea, nausea, stomach cramps, diarrhoea, urticaria/angiodema, diaphoresis, hives, laryngeal oedema, generalised itching and swelling, tingling sensations, flushing, hypotension, cyanosis, shock and loss of consciousness (2). Many of the symptoms mirror those of anaphylaxis. Indeed reactions to sulphites can be life threatening, as a number of fatal cases have been reported (3, 4). In many areas of the world, sulphites are now one of the potential allergens (along with the likes of peanuts, fish, crustaceans, gluten and milk) that have to be labelled on food and drink products. In the European Union (EU), levels in foods and drinks above 10 mg/kg or 10 mg per litre have to be labelled. Warning labels are now commonplace, yet in practice there is still a huge amount of ignorance and misinformation about the use of sulphites in food, drinks and pharmaceutical products. Hence, Clinicians need to be aware of sulphite sensitivity in order to enable appropriate diagnosis and provide recommendations for treatment.

Precautions are recommended in a hospital setting where common pharmaceutical drugs, foods and beverages may cause reactions in sulphite sensitive individuals, particularly as sulphites are used in many commonly used drugs including some formulations of paracetamol, zithromax, epinephrine (5). It would also be important to consider the combined potential exposure a sensitive individual may encounter within a hospital or surgical environment from food, drink and pharmaceutical sources.

A low sulphite diet would be recommended if a sulphite sensitive patient is hospitalised in addition to avoidance of pharmaceutical products containing sulphites wherever possible. Management of a sulphite sensitive individual undergoing anaesthesia also presents particular challenges given sulphites may be in both local anaesthetic agents and epinephrine. It is important to remember risks may also be present for individuals that do not know they have a sulphite sensitivity, for example as in the case report of anaphylactic shock during epidural anaesthesia for caesarean section as a result of exposure to metabisulphite (6).

A report from the World Health Organisation International Programme on Chemical Safety states the ADI is 0 - 0.07 mg/kg body weight (7). In a low sulphite diet levels would need to be minimised as much as possible. This probably represents a major challenge for both clinicians and hospital catering staff given the many widespread and varied uses of sulphites. For example, sulphites can be used to modify the texture of dough, as the breaking of disulphide bonds weakens dough making it suitable

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for crackers and pizza bases (8). Sulphites can also occur naturally in foods and drinks e.g. saccharomyces cerevisiae generates between 1-30 parts per million (ppm) SO2 in fermentation and some strains produce in excess of 100 ppm (9). Levels of sulphites in foods can be as high as over 4,000 ppm, some examples are detailed in the tables 1-5.

Table 1. Examples of high sulphite level foods (>100 ppm SO2) (10)

Wine
Molasses
Sauerkraut
Lemon juice (non-frozen)
Dried fruit (excluding dark raisins and prunes)

Lester (10) classifies a food with a level of 100 ppm SO2 or more as a high sulphite food, foods with a sulphite level of 50 – 99.9 ppm as moderate sulphite level foods and foods with 10 - 49.9 ppm as low sulphite foods (Tables 1-3). These should be avoided as much as possible by a sulphite sensitive individual, who should be counselled on suitable food choices by an appropriate health professional. Nutritional strategies for the management of sulphite sensitive individual would probably need to include the avoidance of many pre-prepared, packaged foods and drinks containing sulphites at levels above 10 mg/kg or 10 mg per litre with specific avoidance of food containing the sulphite additives.

Table 2. Examples of moderate sulphite level foods (50-99.9 ppm SO2) (10)

Dried potatoes
Grape juice
Wine vinegar
Gravies, sauces
Fruit topping
Maraschino cherries

There are eleven different ways of measuring sulphite levels in foods (8). The Optimized Monier-Williams method measure total SO2 (11). The FDA in the U.S.A. uses the Optimized Monier-Williams method for official samples. As sulphites exist in many different forms and as sulphite salts release SO2, sulphite levels are usually expressed as SO2 equivalents (SDE). However, the Optimized Monier-Williams method can give false positives as naturally occurring sulphur chemicals e.g. in brassicas and garlic will yield SO2 readings (8). It is also important to remember that the storage and preparation of foods can also affect the levels of sulphite (11). Sulphites may be lost as a result of autoxidation, for example when a packet or jar is opened and exposed to air (2). Packaging may also affect sulphite levels, as there may be a complete loss of sulphites from plastic bottles, whereas glass bottles seem to prevent the loss of sulphites (2).

Table 3. Examples of low sulphite level foods (10-49.9 ppm SO2) (10)

Pectin
Shrimp (fresh)
Corn starch
Corn syrup
Pickles/relishes
Frozen potatoes
Imported jams and jellies
Maple syrup

Table 4. Sulphite levels in imported foods (8)

Food	Sulphite Levels (ppm SO2)
Dried bamboo shoots	2100
Dried apple	750
Ginger	1900
Sweet coconut	375
Dried abalone	11000
Sun-dried tomatoes	800
Shrimp	600

Normally ingested sulphite is oxidised to sulphate by the enzyme sulphite oxidase (SO) and then excreted in the urine. Approximately 16-24 mmol of inorganic sulphate is excreted daily (2). SO is normally widely distributed in the human body, with the highest amounts found in the liver and kidneys. Hence, it may be likely that pathologies of these organs may increase the likelihood of sensitivity to sulphites. There are several documented cases of sulphite oxidase (SO)

deficiency (12). This was associated with severe neurological abnormalities and retardation. Animal studies of induced SO deficiency, have shown that it increases sensitivity to dietary sulphites (13). Hence, low levels of this enzyme may play a role in sulphite sensitivity in humans. Molybdenum deficiency may be a cause of an apparent case of induced sulphite oxidase deficiency (14). Hence, lack of enzymatic co-factors may also be a contributory factor.

Table 5. Food additives containing sulphites

E Number	Name
E220	Sulphur dioxide
E221	Sodium sulphite
E222	Sodium hydrogen sulphite
E223	Sodium metabisulphite
E224	Potassium metabisulphite
E226	Calcium sulphite
E227	Calcium hydrogen sulphite
E228	Potassium hydrogen sulphite
E150	Sulphited colour caramels (E150 b/d)

A SO2 metabolite (glutathione S-sulfonate) has been demonstrated in studies on rat liver, lung and human lung cells to be a competitive inhibitor of the liver enzyme glutathione S-transferase (GST) (15). Researchers suggested that SO2 may have a detrimental effect on the general detoxification of xenobiotic compounds generally detoxified in the glutathione conjugation pathway, involving GST (15). They suggest it may deplete glutathione supply and it could be a contributory factor in sulphite sensitivity. Obviously, further studies would be required to validate this.

In terms of diagnosis, the literature shows that oral challenge tests and measurements of FEV and FEV at intervals after challenge have been widely used to diagnose sulphite sensitivity. Obviously, it is vital that a clinician takes a full medical history, establishes if the patient is asthmatic/atopic and analyses symptoms associated with a reaction and rules out other factors (e.g. other allergic reaction, histamine contamination or food poisoning). Consideration of appropriate laboratory tests to rule of infection would also be important (16). The clinician may also need to eliminate other factors such as coeliac disease, where diagnosis can also be challenging especially where presentation is atypical (17).

Oral challenges have been undertaken to a variety of sulphites (e.g. sodium MBS and SO2) in both capsule form and in solution. Oral challenge can result in severe reactions; hence they are usually undertaken in a hospital environment. Many studies have reported that IgE tests have been inconclusive, however a specific IgE antibody to sulphites has been reported (18).

Intradermal patch testing and prick testing has also been used to diagnose sensitivity (19, 9). A study was undertaken to determine validity of patch testing for sulphite sensitivity (20). Sulphite sensitivity was confirmed in 12 cases out of the 13 cases (92%). Whilst the sample size is limited, it would seem that patch testing might have potential as a way of diagnosing sulphite sensitivity. Further research would be required in this area.

In terms of clinical management of signs and symptoms, sodium cromoglycate has been shown to block sulphite induced asthma (21). Corticosteroids may also be prescribed in the case of a severe reaction and bronchoconstriction may be treated with nebulisation or bronchodilators. It is important to ensure that any prescribed medication is free from sulphites, as some corticosteroids contain sulphites (e.g. dexametahsone) and many asthma medications (e.g. isoetharine) contain sodium bisulphite (5). The author notes a sulphite free epinephrine inhaler, is available for the management of bronchial asthma is some areas of the world. This may be of use in the management of a sulphite sensitive individual. If IgE mediated reactions are suspected then anti-histamines may be useful.

Oral administration (prior to ingestion of sulphite) of 1-5mg of vitamin B12 (cyanocobalamin) completely or partially blocked bronchoconstriction from sulphite sensitivity in a study of six patients (22). It was proposed that might be due to the role of B12 as a co-factor in sulphite oxidation, where sulphites

are converted to sulphates by the enzyme Sulphite oxidase (SO). A limitation of this study is the small number of subjects however B12 is readily available, economical and administration has few risks hence may be worthy of consideration by the Physician. It is reported that the drug Doxepin also blocked bronchoconstriction caused by sulphites (22).

Sulphite sensitivity whilst rare is serious and consequently clinicians need to be aware of the challenges in diagnosis and treatment. There is undoubtedly a need for interprofessional collaboration to ensure effective diagnosis and management. Best practice in the management of a sulphite sensitive individual is also an important area for future consideration.

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