Sulphur dioxide sensitivity in South African asthmatic children

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Abstract **Sulphur dioxide (SO_2) is a well-known precipitant of asthmatic attacks. Many foodstuffs are preserved with SO_2 and other sulphites. In this study 37 asthmatic children attending the Allergy Clinic at the Red Cross Children's Hospital were challenged with SO_2 in apple juice in a dose similar to that commonly ingested in soft-drinks containing this preservative. The responses of these children were compared with the responses of 22 asthmatics challenged with apple juice alone.**

Sixteen out of 37 children (43,2%) challenged with SO_2 reacted with a fall in forced expiratory volume in 1 second (FEV_1) of more than 10% compared with none of the 22 control asthmatic children challenged with apple juice alone (P = 0,0016). Girls were found to be more sensitive than boys. A 20% or more fall in FEV_1 occurred in 8 (21,6%) of the children challenged with SO_2 compared with none in the control group (P = 0,039). There was an individual variability in the responses of sensitive individuals to the SO_2 challenge. Reactions occurred in spite of maintenance medication and occurred within 5 - 30 minutes of challenge. Since sulphite sensitivity is common in asthmatic children, ingestion of sulphites should be avoided.

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Sulphur dioxide (SO_2), sodium and potassium bisulphite and sodium sulphite are widely used as preservatives in the food industry. They inhibit enzymatic browning in fresh fruit, vegetables and salads, and non-enzymatic browning in dried fruit and vegetables. They have a broad-spectrum antimicrobial action in soft-drinks, wine and maize milling. They are also used for conditioning of flour doughs, as a bleaching agent in maraschino cherries,[1] and as preservatives and anti-oxidants in medications.[2,3]

The effect of these agents on sensitive individuals is well recognised.[4-7] Although asthmatics are mainly affected, non-asthmatics may also be affected,[8] but the incidence of sulphite sensitivity in non-asthmatics is not yet known.

In a previous survey done in Cape Town, 27% of a cohort of children with asthma gave a history of being sensitive to sulphites in soft-drinks.[9] Since sulphite sensitivity appeared to be more common in children than in adults, this study was conducted to determine the incidence of sulphite-sensitive asthmatics (SSAs) in South African children by direct challenge.

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Patients and methods

Fifty-nine chronic asthmatic children aged 5 - 13 years, on maintenance medication who attended the Allergy Clinic at the Red Cross Children's Hospital were studied. All were atopic as evidenced by a positive radioallergosorbent test (RAST) or skin tests to common aero-allergens, and all were familiar with the use of a Vitallograph. Only those children with FEV_1 values equal to or greater than 80% of their predicted values were included.

There were 24 girls and 35 boys. All children were compliant with their medication. Five of the children were steroid-dependent and 5 were being treated with sodium cromoglycate. No patients were on both drugs.

The study was conducted over a period of 3 weeks. Children were assigned to control and test groups by means of a system of random numbers. The test group consisted of 25 children (8 girls and 17 boys), and the control group of 22 children (10 girls and 12 boys) tested at 10, 15 and 30 minutes after the SO_2 challenge. To determine the FEV_1 fall at 5 minutes following an SO_2 challenge, a further group of 12 children (6 girls and 6 boys) were challenged with apple juice and SO_2. Since an FEV_1 fall of more than 10% was not observed in any of the 22 controls challenged with apple juice, further controls were not studied. The results of the test groups were analysed as a single set of results.

Challenge

The children were challenged in a double-blind manner with either pure apple juice or apple juice containing sodium metabisulphite 330 mg/l.

The sodium metabisulphite was obtained from Bromor Foods (Pty) Ltd. Three hundred and thirty milligrams sodium metabisulphite added to 1 litre of apple juice resulted in the challenge drink containing 208 parts per million (ppm) total SO_2 as measured by the modified Monier-Williams method (analysed by the State Health Laboratories). One hundred and ten ppm were present as bound SO_2 and 98 ppm as free SO_2 (analysed at the laboratories of Bromor Foods (Pty) Ltd).

The definitive SO_2 challenge tests were conducted as follows. The baseline forced expiratory volume in 1 second (FEV_1) was measured after which the child was asked to drink 200 ml of the test or control juice. FEV_1 tests were performed pre-challenge, and at 5 minutes, 15 minutes, 30 minutes, 60 minutes and 120 minutes post-challenge. The best of three FEV_1 values was accepted. Children were observed for 2 hours and treated with nebulised fenoterol if a fall in FEV_1 of more than 20% was observed or if the child became clinically distressed.

Pilot study

To assess whether usual asthma medication would affect the results of the SO_2 challenge, a pilot study group of 21 children were challenged after a sulphite-free diet 1 week before the challenge with apple juice or apple juice containing SO_2. Their usual medication was withdrawn 2 days before the challenge. As results of the challenge in these children were not significantly different whether they were on or off treatment, medication was not discontinued for the main study.

SAMJ
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Statistical analyses were performed with Epi-Info 5 and Statgraphics; Fisher's exact test and the chi-square test with Yates' correction were utilised.

Permission for the study was obtained from the parents of the children and from the Ethical Review Committee of the University of Cape Town Medical School.

Results

Magnitude of the fall in FEV_1

Sixteen (43,2%) of the 37 challenged with apple juice containing SO_2 showed a fall in FEV_1 of 10% or more in contrast to none in the control group challenged with apple juice alone ($P = 0,0016$). A fall in FEV_1 of 20% or more occurred in 21,6% of children in the former group ($P = 0,039$) (Table I). Nine (64,3%) of the 14 girls showed a fall in FEV_1 of 10% or more compared with 7 (30,4%) of the 23 boys (Table I). A 20% fall in FEV_1 occurred in 5 (21,7%) of the boys and 3 (21,4%) of the girls. One child required nebulisation soon after ingestion of the drink as she became clinically distressed; she was excluded from the rest of the study. Six patients (3 girls and 3 boys) had a persistent FEV_1 fall of more than 20% at 30 minutes requiring nebulisation with fenoterol.

The mean FEV_1 difference was 11,1% between test and control groups at 15 minutes ($P = 0,012$) and of 17,9% at 30 minutes ($P = 0,00034$) (Fig. 1).

TABLE I.
Percentage of children reacting to an SO_2 challenge

FEV_1 fall	Boys	Girls	Total
> 10%	30,4%	64,3%	43,2%
	7/23	9/14	16/37
> 20%	21,7%	21,4%	21,6%
	5/23	3/14	8/37

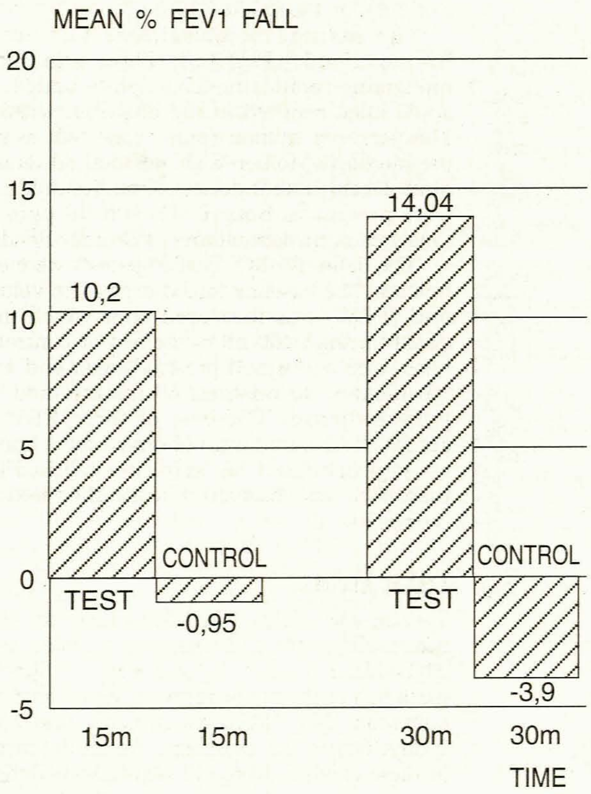

FIG. 1.
Mean FEV_1 fall (%) following a sulphur dioxide challenge.

Variability of onset and recovery of fall in FEV_1

There was a difference in the response to the SO_2 challenge in different individuals in respect of time. Some children reacted to the challenge within 5 minutes and others after a longer period. Spontaneous recovery of the FEV_1 was also variable in different children. More girls reacted within the first 10 minutes after the challenge with an FEV_1 fall of 10% or more, observed in 66,7% (4/6) at 5 minutes post-challenge as compared with 35,7% (5/14) at 15 minutes and 42,9% (6/14) at 30 minutes (Fig. 2). This illustrates the variability of the onset and recovery of their reactions to challenge. This was not apparent in the boys, with a fall in FEV_1 of 10% or more observed in 16,7% (1/6) at 5 minutes, 21,7% (5/23) at 15 minutes, and 17,4% (4/23) at 30 minutes (Fig. 3).

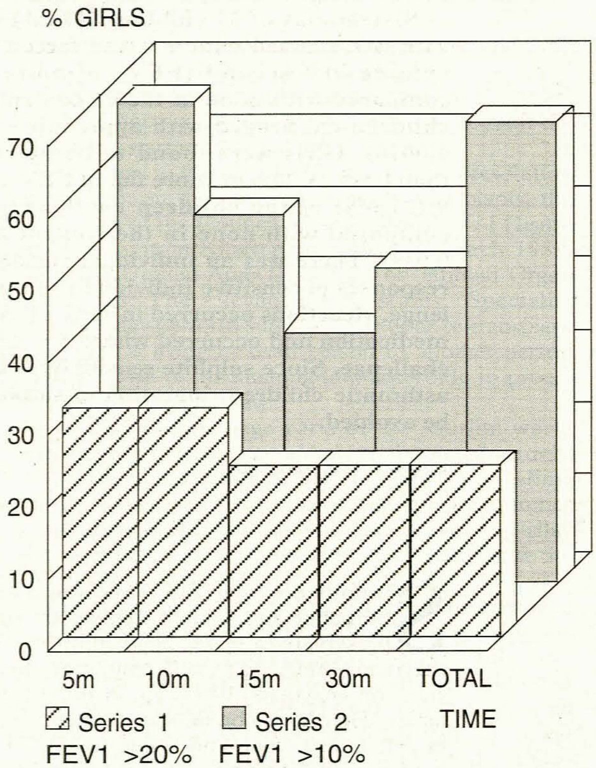

FIG. 2.
Percentage of girls reacting to a sulphur dioxide challenge.

Three patients had an FEV_1 fall of more than 20% from 5 minutes to 30 minutes whereas 1 girl had an FEV_1 greater than 20% at 5 minutes but recovered spontaneously by 10 minutes. Another had an FEV_1 fall of greater than 10% at 15 minutes but recovered by 30 minutes. Two children had a normal FEV_1 at 15 minutes and their FEV_1 only fell at 30 minutes whereas 3 had an FEV_1 fall greater than 10% at 15 minutes but recovered by 30 minutes.

One boy had no fall in FEV_1 but developed severe coughing which only resolved following nebulisation with fenoterol.

Of the 37 children challenged 5 were on steroids (1 girl and 4 boys). Only 2 reacted with an FEV_1 fall of more than 10%. The girl had an FEV_1 fall of 11% at 15 minutes and one boy an FEV_1 fall of more than 20%. Both recovered spontaneously.

Five children challenged with SO_2 were on sodium cromoglycate (4 girls and 1 boy). Three girls had an

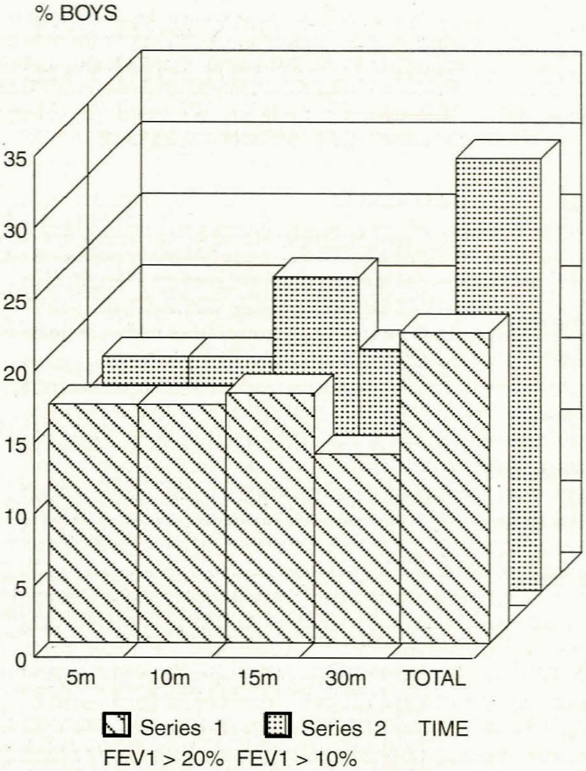

FIG. 3.
Percentage of boys reacting to a sulphur dioxide challenge.

FEV_1 fall greater than 10%, one of which fell more than 20% and required nebulisation with fenoterol. Two remained unaffected.

Discussion

This is the first direct sulphite challenge study performed in South Africa in children with chronic asthma, and objectively confirms and extends our previous report of a high incidence of sensitivity to this food preservative as determined by history alone.[9]

This is also the first study in which the incidence of an FEV_1 fall of 10% or more in asthmatic children challenged with sulphites was determined. The standard employed in previous studies for a significant change following inhalation challenge procedures is an equal to or more than 20% fall in the FEV_1.[10] We have found that the incidence of a fall in the FEV_1 of 10% or more is not only statistically significantly different in the test and control groups, but is also particularly clinically relevant as the majority of these patients were asymptomatic. It is well known that the effect of SO_2 is cumulative and therefore that those children who drink more soft-drinks, e.g. in summer, experience greater falls in FEV_1.

The challenge dose we used represents the approximate dose of SO_2 that a child is likely to ingest when drinking 200 - 250 ml of a soft-drink preserved with it. Levels of this preservative vary between different soft-drinks and even in the same soft-drink, depending on factors such as the freshness of the drink.

The reported prevalence of SSAs varies between 3,9% and 10% in adult asthmatics.[4-7] By contrast two recent studies have reported that 35,3 - 65,5% of children with chronic asthma are SSAs.[11,12] Towns and Mellis[12] found that a challenge with 50 mg of sodium metabisulphite resulted in a more than 20% FEV_1 fall in 19 (66%) of the 29 children in his test group, and 6 (21%) of those children challenged with 25 mg. By contrast, 21% of our children experienced an FEV_1 fall of 20% or more with a dose of 66 mg sodium metabisulphite. Their method of administration delivered all the SO_2 unbound. In our study only 47% of our dose was unbound and this resulted in an effective 31 mg challenge dose.

As in previous studies the onset of reaction occurred within a few minutes to 30 minutes.[4,6,13] We observed a marked variability in the onset of reactions in our SSAs. Some react at 5 minutes, others only later. Furthermore, those who react early may recover spontaneously, or may persist with bronchospasm for 30 minutes or longer. Eight of 37 children whose FEV_1 fell 20% or more appeared to react to the sulphite soon after ingestion, and the fall in FEV_1 was sustained until relieved by nebulisation with fenoterol. Only 1 had resolved spontaneously by 30 minutes.

One child developed a severe coughing spell even though his FEV_1 remained within normal levels. His coughing was relieved by nebulisation with fenoterol. The induction of severe coughing by sulphite challenge requiring β_2-stimulants by means of nebulisation has been described previously.[13]

Delayed reactions can occur after 12 hours,[12] but we did not conduct FEV_1 monitoring beyond 2 hours in our study. Our previous study suggested a dose-dependent effect[9] and this has been confirmed by other studies.[4,6,13]

Only 2 of the 5 children on steroid therapy reacted with an FEV_1 fall of 10% or more, but they resolved spontaneously. Oral and inhaled steroids were not stopped as they are not thought to influence bronchial challenge studies.[14] Previous studies in adults and children have shown that steroid-dependent asthmatics are more sensitive to sulphites.[12,15]

Although sodium cromoglycate has been shown to have a protective effect in some studies,[16-18] 3 of the 5 children in our study were not protected. A similar finding was reported by Dixon.[19] Nedocromil sodium has been shown to be an effective protector against bronchospasm caused by SO_2.[19,20]

The sulphite preservatives are probably the most widely used chemical preservatives, particularly sodium metabisulphite; its active products are SO_2 and bisulphite when in solution. Common foodstuffs that may contain sulphites are listed in Table II.

Several factors determine whether an SSA will react to a foodstuff that contains sulphite. The level of sulphite preservative legally permitted in a foodstuff varies for different foods, and different types of foodstuffs bind SO_2 to varying degrees. An inherent variability in SSAs' reactions to sulphites is also apparent.

It is evident from a number of our patients who remained asymptomatic in the presence of an FEV_1 fall of more than 10%, that a history alone is unhelpful in the diagnosis of an SSA. Objective challenge tests are more reliable for the detection of the child with SO_2 sensitivity, but a history of repeated reactions to foodstuffs that contain SO_2 is clearly helpful.

Although some clinicians may consider it dangerous to challenge asthmatics, we feel that it is probably better to know which children are sensitive than to expose the child to chronic subclinical bronchospasm induced by diet. Obviously patients who are clearly sensitive on history should not be challenged. An SO_2 challenge in children with suboptimal respiratory function can be dangerous and children should only be challenged if their FEV_1 is greater than 80%. We do not consider that routine challenge with SO_2 should be performed in all asthmatics at this stage but would recommend that all asthmatic children avoid foodstuffs that contain SO_2 (Table II).

TABLE II.
Possible sources of sulphites in foodstuffs*†

Food category	Type of food
Beverages	Soft-drinks, fruit juices, grape juice (esp. citrus drinks)
Alcoholic beverages	Wine, beer, cocktail mixes
Condiments	Wine, vinegar, pickles, salad dressings
Confections	Molasses
Dips	Avocado and other dips
Fish	Canned or fresh shrimps, shellfish
Fresh fruit/vegetables	Grapes, fresh pre-cut potatoes
Gravies	Gravies, sauces
Processed fruits	Dried fruit, fruit juice concentrates, purees, dried coconut
Processed vegetables	Instant mashed potatoes, restaurant salad bars, dried vegetables, canned or pickled vegetables, salad dressings, purees
Processed meats	Sausage (boerewors), cold meats, pâté
Puddings	Fruit fillings, gelatin
Grain products	Cornstarch, gravies, noodle rice mixtures
Jams, jellies	Jams, jellies
Snack foods	Dried fruit snacks
Soups	Dried or canned soups
Sweet sauces/syrups	Molasses, pancake syrup, corn or maple syrup

* Full list of soft-drinks in Steinman and Weinberg.[9]
† Sulphites include: sulphur dioxide, sodium or potassium bisulphite, sodium or potassium metabisulphite, sodium sulphite.

Acute bronchospasm induced by SO_2 usually responds to inhaled β_2-agonists. Howland and Simon[13] suggest that SSAs who are seriously affected should probably carry adrenaline inhalers (Medihaler-Epi) with them to treat possible severe reactions.

Education and avoidance of foodstuffs containing sulphites remain the mainstay of treatment, but hidden unlabelled sources are still a problem in South Africa. This problem is at present being actively addressed by food legislating groups and we are lobbying for stricter food labelling practices.

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REFERENCES

1. Taylor SL, Higley NA, Bush RK. Sulfites in food: uses, analytical methods, residues, fate, exposure assessment, metabolism, toxicity, and hypersensitivity. *Adv Food Res* 1986; **30:** 1-76.
2. Settipane GA. Adverse reactions to sulfites in drugs and foods. *J Am Acad Dermatol* 1984; **10:** 1077-1080.
3. Settipane GA. Updated list of sulfites in drugs and foods. *NER Allergy Proc* 1984; **5:** 243-245.
4. Taylor SL, Bush RK, Selner JC, *et al.* Sensitivity to sulfited foods among sulfite-sensitive subjects with asthma. *J Allergy Clin Immunol* 1988; **81:**1159-1167.
5. Bush RK, Taylor SL, Busse W. A critical evaluation of clinical trials in reactions to sulfites. *J Allergy Clin Immunol* 1986; **78:** 191-202.
6. Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthma subjects. *J Allergy Clin Immunol* 1981; **68:** 26-32.
7. Simon RA. Sulfite sensitivity. *Ann Allergy* 1986; **56:** 281-288.
8. Celeste A. Update on sulfites. *Assoc Food Drug US Off Q Bull* 1986; **50:** 46.
9. Steinman HA, Weinberg EG. The effects of soft-drink preservatives on asthmatic children. *S Afr Med J* 1986; **70:** 404-406.
10. Chai H, Farr RS, Forelich LA, *et al.* Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 1975; **56:** 323-327.
11. Friedman ME, Easton JG. Prevalence of positive metabisulfite challenges in children with asthma. *Pediatr Asthma Allergy Immunol* 1987; **1:** 53.
12. Towns SJ, Mellis CM. The role of acetylsalicylic acid and sodium metabisulfite in chronic childhood asthma. *Pediatrics* 1984; **73:** 631.
13. Howland WC, Simon RA. Sulfite-treated lettuce challenges in sulphite-sensitive subjects with asthma. *J Allergy Clin Immunol* 1989; **83:** 1079-1082.
14. Weber RW, Hoffman M, Raine DA, *et al.* Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol* 1979; **64:** 32-36.
15. Bush RK, Taylor SL, Holden K, Nordlee JA, Busse W. Prevalence of sensitivity to sulfiting agents in asthmatic patients. *Am J Med* 1986; **81:** 816-820.
16. McClellan MD, Wanger JS, Cherniack RM. Attenuation of the metabisulfite-induced bronchoconstrictive response by pretreatment with cromolyn. *Chest* 1990; **97:** 826-830.
17. Koenig JQ, Marshall SG, Van Belle G, *et al.* Therapeutic range cromolyn dose-response inhibition and complete obliteration of SO_2-induced bronchoconstriction in atopic adolescents. *J Allergy Clin Immunol* 1988; **81:** 897-901.
18. Nichol GM, Nix A, Chung KF, Barnes PJ. Characterisation of bronchoconstrictor responses to sodium metabisulphite aerosol in atopic subjects with and without asthma. *Thorax* 1989; **44:** 1009-1014.
19. Dixon CMS, Fuller RW, Barnes PJ. The effect of nedocromil sodium on sulphur dioxide-induced bronchoconstriction. *Thorax* 1987; **42:** 462-465.
20. Dixon CMS, Ind PW. Metabisulphite-induced bronchoconstriction: mechanisms. *Am Rev Respir Dis* 1988; **137**(4) Part 2, suppl: 238.