Attenuation of the Metabisulfite-induced Bronchoconstrictive Response by Pretreatment with Cromolyn*


In a retrospective analysis of 1,544 patients who underwent provocative challenge with metabisulfite at the National Jewish Center between 1983 and 1987, an abnormal airway response to metabisulfite was found in 52 patients, an incidence of 3.4 percent. There was no relationship between this abnormal airway responsiveness to metabisulfite and the degree of airway obstruction present, or the degree of airway reactivity as assessed by the response to inhaled bronchodilator or exercise testing. In a pilot study, we found that the administration of cromolyn sodium prior to metabisulfite challenge markedly attenuated the abnormal bronchoconstrictive response in nine of ten patients. We conclude that a metabisulfite-induced bronchoconstrictive response cannot be predicted on the basis of the degree of airway obstruction or airway reactivity and that pretreatment with cromolyn sodium may attenuate the abnormal response. (Chest 1990; 97:826-30)

It is well recognized that abnormal reactions, including pruritis, urticaria, angioedema, asthma, and anaphylaxis can occur after the ingestion of sulfite agents, which are contained in many foods, drinks, and medications. Unfortunately, the likelihood of enhanced sensitivity to sulfites is not generally predictable on the basis of historic information, skin tests, serum IgE levels, or blood eosinophil levels. Therefore, provocative challenges (ingestion or inhalation) are utilized to evaluate sulfite sensitivity. The mechanism underlying the increased airway reactivity to metabisulfites and the relationship to the degree of obstruction to airflow or airway reactivity has not been elucidated. In addition, management of sulfite sensitivity has not been satisfactory since "avoidance of sulfites" is difficult.

The purpose of this article is to report the findings in a series of patients with abnormal airway sensitivity to metabisulfites and (1) to determine the relationship between a metabisulfite-induced bronchoconstrictive response and the degree of airflow obstruction or airway reactivity, as assessed by the improvement in pulmonary function following inhaled bronchodilator or deterioration following exercise, and (2) to determine in a pilot study, the effect of pretreatment with cromolyn sodium.

**Materials and Methods**

From November 1983 to November 1987, 1,544 patients underwent provocative challenge with metabisulfite at the National Jewish Center for Immunology and Respiratory Medicine. In all patients, tests were performed after inhaled β-adrenergic agonists were withheld for four to six hours, cromolyn sodium for 48 hours, antihistamines for 72 hours, and atropine for 24 hours. In patients with a history suggestive of a metabisulfite reaction, 5 mg/ml of the metabisulfite dose was administered initially, followed by 25, 50, and 100 mg at 30-minute intervals. In all other patients, an initial dose of 25 mg was followed by 50 and 100 mg at 30-minute intervals. Each dose was diluted in 200 ml of natural carrot juice (the least acid of the natural juices readily available) and sipped over a 60-second period. Baseline measurements of spirometry were followed by repeat testing at 5, 15, and 30 minutes after each dose. A fall in FEV, of at least 20 percent was considered a positive response, and the lowest concentration of metabisulfite that resulted in this fall in FEV, was recorded as the provocative dose.

In all patients who demonstrated a positive response to metabisulfite, a placebo challenge using the same diluent was carried out over the same time period as the metabisulfite challenge within the next three days. A bronchoconstrictive response to metabisulfite and failure to respond to placebo was found in 52 patients, an incidence of 3.4 percent. In 49 of these 52 patients, the degree of reduction in airflow limitation after inhaled bronchodilator was assessed; and in 33 patients, exercise challenge was carried out to determine whether exercise-induced bronchospasm was present. Exercise was performed on a treadmill (Quintron 6000), with imposition of a workload that was increased over the first three minutes to achieve a target heart rate of 80 to 85 percent of the predicted maximum, and then maintained at this load for four to six minutes.

**Table 1—Spirometric Characteristics of Patients with Abnormal Metabisulfite Sensitivity**

<table>
<thead>
<tr>
<th>Data</th>
<th>n</th>
<th>Mean ± SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52</td>
<td>36.1 ± 2.0</td>
<td>8-71</td>
</tr>
<tr>
<td>Baseline FEV, L</td>
<td>52</td>
<td>2.35 ± 0.11</td>
<td>0.91-4.44</td>
</tr>
<tr>
<td>Percent change in FEV,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With bronchodilator</td>
<td>49</td>
<td>35.7 ± 7</td>
<td>−6 to +236</td>
</tr>
<tr>
<td>With exercise</td>
<td>33</td>
<td>−21.9 ± 3</td>
<td>+10 to −48</td>
</tr>
</tbody>
</table>

*Provocative dose (lowest dose at which there was at least 20 percent decline in FEV,) of metabisulfite was 100 mg in 20 patients, 50 mg in 15 patients, and 25 mg in 17 patients.

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Manuscript received June 23, revision accepted September 19.

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The relationship between the response to inhaled bronchodilator and the provocative dose of metabisulfite in 49 patients is shown in Figure 2. There was no statistically significant relationship ($p > 0.3$) between the provocative dose of metabisulfite and response to inhaled bronchodilator, although there was a tendency for the response to bronchodilator to be less in patients who responded at the higher doses.

The relationship between the degree of airway reactivity as assessed by the change in FEV$_1$ following exercise and the provocative dose of metabisulfite in 33 patients is shown in Figure 3. Again, no relationship ($p > 0.1$) between the decline in FEV$_1$ following exercise and the provocative dose of metabisulfite was observed.

Figure 4 depicts the effect of pretreatment with cromolyn prior to metabisulfite challenge in ten patients. In all patients the baseline FEV$_1$ was equivalent on the different challenge days. In each case the change in FEV$_1$ following metabisulfite with cromolyn pretreatment is compared to that at the provocative dose of metabisulfite without cromolyn. As can be seen, there was a marked reduction in metabisulfite-induced bronchoconstriction following pretreatment with cromolyn in nine of the ten patients.

Since it was possible that the reduced response to metabisulfite could be due to desensitization by the repeated tests, a third metabisulfite challenge was carried out in one patient (patient 8). The initial challenge with metabisulfite (1) was followed by placebo challenge (2), then by metabisulfite after pretreatment with cromolyn (3), and finally the third challenge with metabisulfite (4). The results of the challenges on four different days are shown in Figure 5. As can be seen, there was no evidence of desensitization, as the abnormal response to metabisulfite persisted and was present after the administration of cromolyn sodium had obviated the fall in FEV$_1$.

Analysis of Data

The dose of metabisulfite which induced a fall in FEV$_1$ of 20 percent or greater and the degree of obstruction and response to bronchodilator or exercise were compared with a one-way analysis of variance for multiple experimental groups. A value for $p$ of less than 0.05 was considered significant.

RESULTS

The degree of airflow limitation as reflected by the FEV$_1$ is compared to the provocative dose of metabisulfite in the 52 patients who demonstrated an abnormal response in Figure 1. There was no relationship ($p > 0.1$) between the degree of airflow limitation and the dose of metabisulfite that invoked a positive reaction.

Figure 1. Degree of airflow limitation (baseline FEV$_1$ ± SEM) is plotted against provocative dose of metabisulfite. Severity of sensitivity to metabisulfite does not correlate with degree of airflow limitation.

Figure 2. Airway reactivity (percentage of increase in FEV$_1$ following bronchodilator ± SEM) is plotted against provocative dose of metabisulfite. Severity of sensitivity to metabisulfite does not correlate with degree of airway reactivity.
following metabisulfite.

**DISCUSSION**

It is well recognized that severe asthmatic attacks and anaphylaxis can occur following metabisulfite exposure in sensitive patients. Our finding of an abnormal sensitivity to metabisulfite in 52 of 1,544 patients evaluated at the National Jewish Center represents an incidence of 3.4 percent and was found over a broad age spectrum (8 to 71 years); however, this is likely an underestimate of the true prevalence of sensitivity to metabisulfite, as the criteria for challenge were not controlled. It is also possible that our incidence is an overestimate of the true prevalence of hypersensitivity to metabisulfite, because of the nature of the patients who are referred to the National Jewish Center. For the most part, the challenges were carried out in patients with chronic asthma, but some of the patients may have been suffering from other diseases. Nevertheless, the incidence in our patients is similar to that estimated by Buckley et al. and Bush et al., but is slightly lower than the 8 percent reported by Simon et al. and markedly below the 66 percent observed in children with asthma by Towns.
and Mellis.\textsuperscript{14}

The search for an abnormal response to metabisulfite is frequently reserved for patients with severe airway hyperreactivity. Our data indicate that a patient's history and physiologic disturbances may not reliably predict an exaggerated response to metabisulfite. There was no relationship between the severity of metabisulfite sensitivity (as reflected by the dose which induced an abnormal response) and the degree of airflow limitation present, or airway reactivity, as assessed by either the response to inhaled bronchodilator or to exercise testing. Thus, our data suggest that abnormal metabisulfite sensitivity should be sought even in patients without severe or recalcitrant airway reactivity.

The management of the patient who demonstrates an abnormal responsiveness to metabisulfite is difficult.\textsuperscript{2,5,8,10} Total avoidance of metabisulfites is unrealistic, since sulfites have been used extensively for years as preservatives, sanitizing agents, and antioxidants and therefore are contained in many foods, drinks, and drugs.\textsuperscript{3,15} Protective measures aimed at obviating metabisulfite sensitivity are clearly desirable, and a variety of agents have been utilized in an attempt to block metabisulfite-induced bronchoconstriction.\textsuperscript{16-20} In this pilot study, we have found that pretreatment with cromolyn obviated or reduced the bronchoconstrictive response to metabisulfite in nine of the ten subjects studied. It is possible that a higher dose of cromolyn may have resulted in blockade or partial blockade of the response to metabisulfite in the remaining patient. Indeed, recent studies by Koenig et al\textsuperscript{21} and Myers et al\textsuperscript{22} suggest that the protective effect of cromolyn might be dose-related. Thus, the data presented indicate that the effect of pretreatment with cromolyn sodium in patients who have abnormal metabisulfite sensitivity may provide protection against bronchoconstriction. Although only carried out in one patient (patient 8), repeat challenge with metabisulfite indicates that pretreatment was effective and that the improvement was not due to desensitization.

The mechanism by which cromolyn protects against a fall in FEV\textsubscript{1} following metabisulfite is not readily apparent. Stabilization of mast cell membranes by cromolyn with subsequent effects on mediator release is well documented;\textsuperscript{23-28} however, it is likely that cromolyn has multiple effects in addition to mast cell stabilization, as is exemplified by its effectiveness in blocking bronchospasm induced by exercise,\textsuperscript{26,27} cold air exposure,\textsuperscript{29} occupational exposures,\textsuperscript{29} and allergen exposure.\textsuperscript{30-33} It is also possible that cromolyn may block the reflex reaction involving stimulation of irritant receptors by metabisulfite.\textsuperscript{29,31}

Whatever the mechanism of action, this pilot study suggests that an abnormal response to metabisulfite may be present in a significant proportion of patients with chronic airflow limitation, and that cromolyn sodium may obviate this response; however, a double-blind placebo-controlled study will be necessary to confirm cromolyn's effect on metabisulfite-induced bronchospasm.

ACKNOWLEDGMENTS: We thank Ms. Cynthia Cooper for performing the metabisulfite challenges and Ms. Sue Hirsch and Ms. Cindi Houk for their assistance in the preparation of the manuscript.

\textbf{FIGURE 5.} Plot of FEV\textsubscript{1} against time in one patient (patient 8) on four different challenge days. First challenge (1, open squares) represents metabisulfite-induced bronchoconstriction at 25 mg. Second challenge (2, open circles) is placebo inhalation challenge. Third challenge (3, solid squares) represents metabisulfite challenge after pretreatment with cromolyn. No significant bronchoconstriction occurred. Fourth challenge (4, open squares) was repeat metabisulfite challenge. Again, bronchoconstriction occurred after challenge with 25 mg. In this patient, desensitization to metabisulfite does not explain protective effect of cromolyn.
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