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Protective effect of drugs on bronchoconstriction induced by sulphur dioxide

WC TAN, E CRIPPS, N DOUGLAS, MF SUDLOW

From the University Department of Respiratory Medicine, City Hospital, Edinburgh

ABSTRACT The response to inhaled sulphur dioxide in eight normal, seven atopic, and 22 asthmatic subjects was studied by measuring thoracic gas volume and airway resistance in a whole-body plethysmograph. The fall in specific airway conductance in relation to the concentration of sulphur dioxide inhaled (0–20 ppm) was determined in all three groups. The specific airway conductance fell significantly in the atopic and asthmatic subjects but not in the normal group. In a double-blind study prior inhalation of disodium cromoglycate caused a significant reduction in the response to sulphur dioxide inhalation in atopic and asthmatic subjects. Prior treatment with inhaled ipratropium bromide blocked the response in the atopic subjects, but the effect was variable in the patients with asthma. Previous treatment with inhaled clemastine also reduced the response in patients with asthma, without causing a change in baseline specific conductance. We conclude that non-allergic bronchial hyperreactivity was increased in the atopic and the asthmatic subjects and that mediator release, in addition to a vagal reflex, has a role in such bronchoconstriction.

Non-allergic bronchial reactivity is usually assessed as the bronchomotor response to pharmacological agents such as methacholine and histamine.[1,2] Inhalation of sulphur dioxide has been shown to produce an increase in bronchomotor tone in healthy people[3,4] and in patients with asthma.[5] Our study was designed to assess this response in normal subjects, atopic non-asthmatic subjects, and patients with asthma.

The changes in bronchomotor tone induced by sulphur dioxide may result from a vagal reflex[3,4] or from mediator release from mast cells. To investigate this further we measured the influence of an anticholinergic drug (ipratropium bromide), disodium cromoglycate, and an antihistamine drug (clemastine) on bronchoconstriction induced by sulphur dioxide.

Subjects

We studied eight normal subjects (five men and three women, aged 20–42 years), seven atopic subjects (five men and two women, aged 29–42 years) and 22 patients with asthma (14 men and eight women, aged 16–60 years). The normal subjects were healthy volunteers. The atopic subjects gave positive responses to house dust mite extract and at least one other common environmental allergen in skin prick tests. All gave a history of seasonal or perennial rhinitis but no previous history of episodic wheeze. The FEV_1 and forced vital capacity (FVC) were within normal limits. The patients with asthma had a recent history of episodic wheezing and dyspnoea, positive responses in skin prick tests to house dust mite and other allergens, and evidence of an increase in FEV_1 of greater than 20% after inhaling a sympathomimetic bronchodilator.

Each study was carried out at the same time of the day and the series was completed in six to eight weeks for each subject. No test was carried out on a subject within six weeks of a respiratory tract infection.

All asthmatic patients were receiving sympathomimetic bronchodilators; three were receiving beclomethasone dipropionate aerosol and two disodium cromoglycate. Bronchodilator treatment was withheld for 12 hours and topical steroids and cromoglycate for at least 24 hours. Antihistamines were withheld for 72 hours before the studies in the atopic subjects. The study was approved by the South Lothian District ethical advisory committee and informed consent was obtained from all the subjects.

Address for correspondence: Dr WC Tan, Department of Medicine (I), Singapore General Hospital, Singapore 0316 (no reprints will be available).

Method

Dry sulphur dioxide gas (SO_2) at 40 parts per million (ppm) was mixed with oxygen in a glass chamber to give sulphur dioxide concentrations ranging from 0 to 20 ppm, measured by a pulsed fluorescent SO_2 analyser (Thermo Electron Model 40).

In the first study each subject inhaled concentrations of sulphur dioxide increasing from 2·5 ppm to 20 ppm for five minutes at each concentration. Thoracic gas volume (TGV) and airway resistance (Raw) were measured in a whole-body plethysmograph (Fenyves and Gut, Basle) before and immediately after exposure to each concentration and at five-minute intervals for the next 15 minutes. Dose-response curves were thus obtained for each subject. In all subsequent studies the subject inhaled the concentration of sulphur dioxide that had previously given either the greatest fall or at least a 30% fall in specific airway conductance (sGaw). In the normal and atopic subjects this concentration was 20 ppm, but in the asthmatic subjects it was 10 ppm. The mean of five readings was taken for each measurement of Raw and TGV. All values of Raw were converted to specific airway conductance. The response to sulphur dioxide inhalation was expressed as the fall in sGaw as a percentage of the baseline value.

The bronchoconstrictor response to a single concentration of sulphur dioxide as determined above was studied in seven atopic and nine asthmatic subjects before and 60 minutes after inhaling 80 μg of an aerosol of ipratropium bromide from a metered dose inhaler (Atrovent). In a separate study six normal, five atopic and 18 asthmatic subjects were studied after prior treatment with either placebo (lactose) or disodium cromoglycate. In this double-bind trial each subject received either one lactose (20 mg) or one disodium cromoglycate (20 mg) spincapsule at six-hour intervals for 24 hours before the test. The last dose was given half an hour before the test. Seven of the asthmatic patients were also studied after inhalation of either 0·9% saline or 1 mg/ml clemastine. Two millilitres of either solution, given in random order, was nebulised from an Inspiron nebuliser at a flow rate of 10 l/min 10 minutes before inhaling 10 ppm of sulphur dioxide. The weight of clemastine nebulised was 1–2 mg.

The results were analysed by the Wilcoxon two-sample and Wilcoxon signed-rank tests as normality of distribution could not be assumed. Values were expressed as means ± SEM.

Results

The maximal fall in sGaw occurred within five minutes of the inhalation of sulphur dioxide in all the subjects studied. sGaw returned to the baseline value within 15 minutes of the inhalation in normal subjects. In the asthmatic patients and some atopic subjects the fall in sGaw was more sustained, sometimes persisting beyond 30 minutes (fig 1).

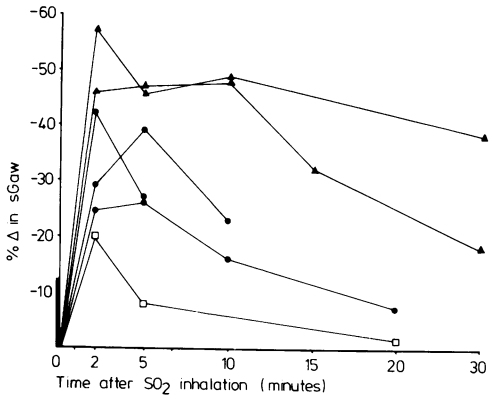

Fig 1 *Individual time-response curves to sulphur dioxide in the one normal, three atopic, and two asthmatic subjects.* □—□ *normal;* ●—● *atopic;* ▲—▲ *asthmatic.*

The mean baseline values of sGaw before sulphur dioxide inhalation were 1·71 ± 0·23 $kPa^{-1}s^{-1}$ in the normal group, 2·03 ± 0·26 $kPa^{-1}s^{-1}$ in the atopic group, and 1·09 ± 0·10 $kPa^{-1}s^{-1}$ in the asthmatic subjects. The mean baseline value in the asthmatic patients was significantly lower than those in the normal and atopic subjects ($p < 0·01$). After sulphur dioxide inhalation the lowest sGaw in the normal group was 1·59 ± 0·12 $kPa^{-1}s^{-1}$ after 10 ppm and 1·52 ± 0·07 $kPa^{-1}s^{-1}$ after 20 ppm, giving maximal percentage falls of 7·2 ± 4·68% and 12·8 ± 5·24%. In the atopic subjects the lowest sGaw after 10 ppm sulphur dioxide was 1·28 ± 0·16 1 and after 20 ppm it was 1·23 ± 0·16 $kPa^{-1}s^{-1}$. The percentage falls were 25·3 ± 2·33% and 39·5 ± 4·89%. In the asthmatic patients the lowest sGaw after 10 ppm sulphur dioxide was 0·67 ± 0·09 1, giving a fall in sGaw of 42·2 ± 4·39% (fig 2). At 10 ppm and 20 ppm the mean percentage falls in sGaw in the atopic subjects were significantly greater than those in the normal subjects ($p < 0·01$). At 10 ppm the percentage fall in the asthmatic patients was also significantly greater than in the normal subjects ($p < 0·001$). The difference between the atopic and asthmatic subjects in the mean percentage falls in sGaw did not, however, reach significance.

EFFECT OF IPRATROPIUM BROMIDE ON THE RESPONSE TO SULPHUR DIOXIDE INHALATION

One hour after inhaling 80 μg of ipratropium bromide the mean baseline sGaw in seven atopic

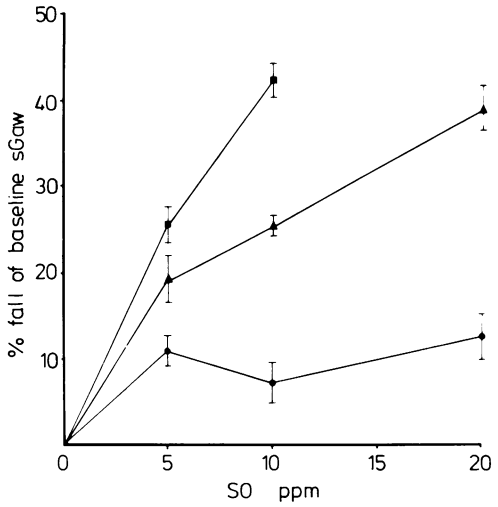

Fig 2 *Fall in sGaw, expressed as percentage of baseline value, after sulphur dioxide inhalation (5 ppm to 20 ppm) in eight normal, seven atopic, and 22 asthmatic subjects. Values expressed as means ± 1 SEM. ● normal; ▲ atopic; ■ asthmatic.*

subjects increased slightly from 2·53 ± 0·32 $kPa^{-1}s^{-1}$ to 2·94 ± 0·48 $kPa^{-1}s^{-1}$ in the atopic subjects ($p > 0·05$), and significantly from 0·86 ± 0·04 $kPa^{-1}s^{-1}$ to 1·38 ± 0·05 $kPa^{-1}s^{-1}$ in the nine asthmatic patients ($p < 0·01$). In the atopic subjects ipratropium bromide reduced the fall in sGaw after 20 ppm sulphur dioxide from 43·3 ± 6·48% to 16·92 ± 7·52% ($p < 0·05$) (fig 3). In the asthmatic patients the individual responses to 10 ppm were variable (fig 4), but the mean fall in sGaw after sulphur dioxide inhalation was significantly reduced from 54·14 ± 4·59 $kPa^{-1}s^{-1}$ before treatment to 35·9 ± 7·99 $kPa^{-1}s^{-1}$ after ipratropium ($p < 0·05$).

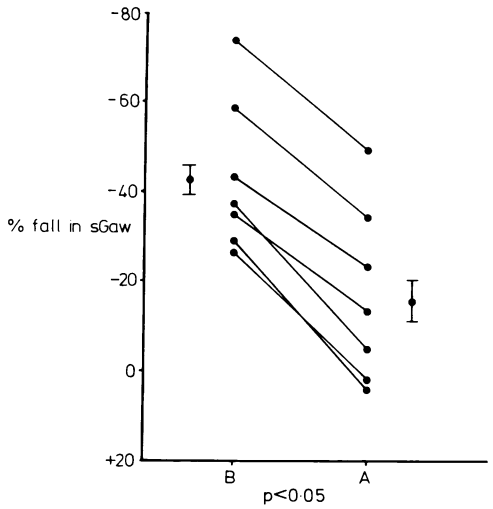

Fig 3 *Fall in sGaw after 20 ppm sulphur dioxide inhalation in seven atopic subjects before and after treatment with ipratropium (80 μg). B — before ipratropium; A — after ipratropium. The two vertical bars indicate means ± 1 SEM.*

EFFECT OF DISODIUM CROMOGLYCATE ON RESPONSE TO SULPHUR DIOXIDE INHALATION

The fall in sGaw after inhalation of 20 ppm sulphur dioxide in the six normal subjects was 16·9 ± 6·37% with placebo compared with 11·1 ± 3·58% with disodium cromoglycate; in the five atopic subjects the fall was 39·3 ± 9·02% with placebo and 19·7 ± 17·7% with disodium cromoglycate. The responses to 10 ppm sulphur dioxide in the 18 asthmatic patients were 41·7 ± 3·94% with placebo and 26·4 ± 5·00% with disodium cromoglycate. These differences were significant in the atopic and asthmatic subjects ($p < 0·01$) but not in the normal subjects.

EFFECT OF CLEMASTINE ON THE RESPONSE TO SULPHUR DIOXIDE INHALATION

In seven asthmatic patients the fall in sGaw produced by 10 ppm sulphur dioxide after inhalation of 1·02 ± 0·19 mg of clemastine was 38·9 ± 11·7%. This was significantly less than the fall after inhala-

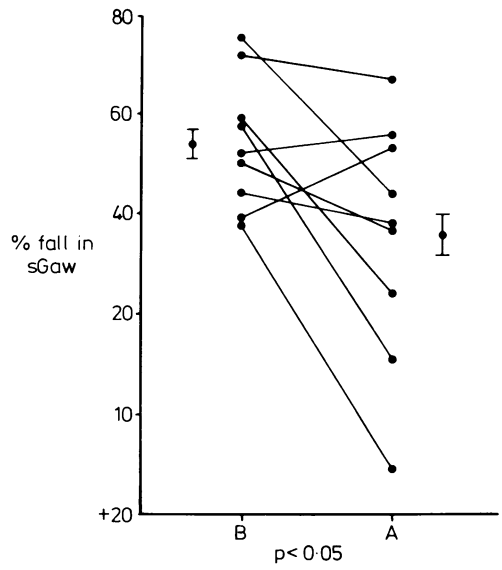

Fig 4 *Fall in sGaw after 10 ppm sulphur dioxide inhalation before and after treatment with ipratropium (80 μg) in nine asthmatic patients. B — before ipratropium; A — after ipratropium. The two vertical bars indicate means ± 1 SEM.*

tion of 0·9% saline—58·4 ± 4·9% ($p < 0·01$; fig 5). There was no difference in the baseline value of sGaw after either clemastine (0·96 ± 0·14 $kPa^{-1} s^{-1}$) or saline inhalation (1·06 ± 0·12 $kPa^{-1}s^{-1}$).

Discussion

Bronchial hyperreactivity to non-allergic stimuli is well known in allergic subjects[1 6 7] and is shown by the progressive increase in sensitivity to sulphur dioxide challenge from the normal subjects to the atopic non-asthmatic subjects and from these to the patients with asthma. This increased bronchial reactivity produced by sulphur dioxide in the atopic subjects in our study agrees with the histamine bronchial reactivity in allergic non-asthmatic subjects reported by others.[6 7] Interestingly, Sheppard *et al*[9] did not find any change in the airway resistance during or after inhaling 1, 3, or 5 ppm sulphur dioxide in the atopic subjects, nor could Harris[8] find any change in FEV_1 in atopic subjects. This difference from our findings could be explained by the fact that we used higher sulphur dioxide concentrations than Sheppard *et al*[9] in our atopic subjects and that a change in specific airway conductance may be a more sensitive indicator than a change in FEV_1.

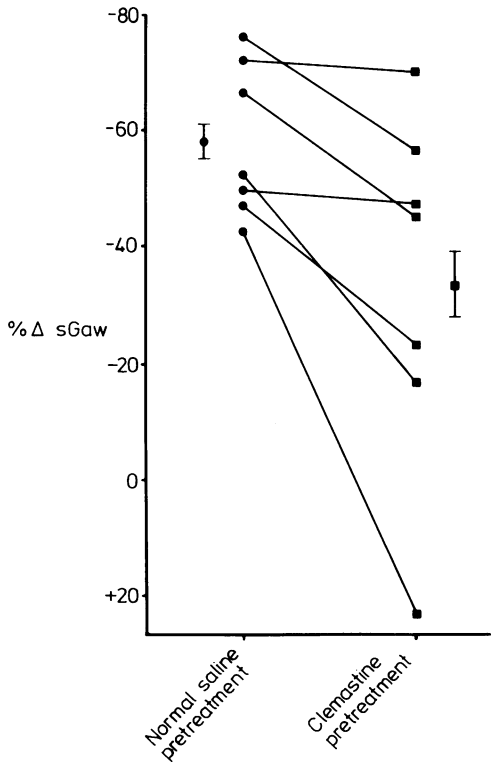

Fig 5 *Fall in sGaw after 10 ppm sulphur dioxide inhalation following treatment with either normal saline or clemastine in seven asthmatic patients. The two vertical bars indicate means ± 1 SEM.*

The mechanism of bronchial hyperreactivity is unresolved. Change in resting airway calibre has been implicated as one factor.[10] This is unlikely to be a major influence in bronchoconstriction induced by sulphur dioxide as our normal and atopic subjects had similar baseline sGaw but significantly different responses to sulphur dioxide. Both animal[11] and human[12] studies suggest that a cholinergic reflex is concerned in the bronchoconstriction resulting from the inhalation of particulate or gaseous irritants. In the present study the atopic subjects had a significant reduction in bronchoconstriction induced by sulphur dioxide after ipratropium, which suggests a vagal reflex in its causation.[3 4] Ipratropium bromide could, however, have left the airway smooth muscle relaxed and less responsive to constrictor influence.[10] In the asthmatic subjects ipratropium bromide had a variable effect, which was difficult to interpret as the drug itself caused bronchodilation so that the sulphur dioxide challenge was inevitably not given under comparable conditions. The between-subject variability in the inhibition by ipratropium bromide of bronchoconstriction induced by sulphur dioxide could be due to variable amounts of the drug inhaled; but, perhaps more likely, it could have reflected the relative importance of the cholinergic pathway in different subjects. Similar variations have been reported in exercise-induced asthma.[13]

Disodium cromoglycate has been observed to attenuate the bronchoconstriction resulting from irritants[5] and other non-allergic triggers, including methacholine[14] and exercise[15] in patients with asthma. Our results showed that this was true for bronchoconstriction induced by sulphur dioxide. We also found that disodium cromoglycate reduced this bronchoconstriction in atopic non-asthmatic subjects, which suggests that the same mechanisms were at work in atopic subjects and asthmatic patients.

The effect of disodium cromoglycate on bronchoconstriction induced by non-allergic triggers raises the possibility that the drug also acts on cholinergic or irritant receptors.[14] Dixon *et al*,[16] however, using single fibre preparations from a dog vagus, found that histamine-induced discharge from irritant receptors was not reduced by pretreatment with disodium cromoglycate, though discharges conducted along non-myelinated C fibres were reduced.

It had been suggested that the effect of disodium

cromoglycate on induced bronchoconstriction is related to the phosphodiesterase-inhibiting action[17] identified by Lavin *et al.*[18] Our results suggest that this is unlikely to be the cause of the reduced bronchial reactivity after treatment with disodium cromoglycate as the baseline value of sGaw did not change significantly after the drug had ben given.

Clemastine, a selective H_1-antagonist with no anticholinergic or antiserotonic activity,[19] attenuated the bronchoconstriction in response to inhalation of sulphur dioxide in our asthmatic patients. This suggests that histamine was released by mast cells in response to inhalation of sulphur dioxide, but we have no direct evidence of such release of mediators. This observation could, however, imply that the protection afforded by disodium cromoglycate against bronchoconstriction in response to sulphur dioxide challenge arose from the well-known effect of the drug in blocking mast cell degranulation,[20] with no necessity of invoking other effects.[14] The prolonged bronchoconstriction due to sulphur dioxide inhalation observed in some asthmatic patients in our study also supports the belief that mediator release may play a part.

We conclude that in addition to the vagal reflex mediator release from mast cells has a role in bronchoconstriction induced by sulphur dioxide. This may be initiated directly by sulphur dioxide or after the release of histamine or other mediators that have been shown to stimulate irritant receptors in animals.[21] Studies in man using anticholinergics to block the bronchoconstrictor effect of histamine[22] suggest that this may also occur in man.

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