

Role of the oesophagus in asthma induced by the ingestion of ice and acid

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ABSTRACT Twelve Asian patients with a history of asthma exacerbated by ingestion of ice and acidic drinks were selected for study. To determine the site of response to ingested ice and acid they were challenged with ice or dilute hydrochloric acid, which was orally retained on one day and swallowed on another. On a third day a placebo was given. The airway response was assessed by measuring FEV₁ and the provocative concentration of histamine that reduced the FEV₁ by at least 20% (PC₂₀). There was no significant change in FEV₁ or histamine PC₂₀ after placebo or the orally retained challenges for the group as a whole or for any individual. After the ice and hydrochloric acid had been swallowed there was a small but statistically significant mean fall in FEV₁, increasing to a maximum 90 minutes after ingestion, together with a significant increase in bronchial responsiveness. As conditioning of the inspired air would have been similar after orally retained and after swallowed ice or acid, the response is likely to be due to oesophageal stimulation. The mechanism of the response to oesophageal stimulation is unclear, but the slow time course seems to preclude a simple neural reflex.

Ingestion of ice¹ and of dilute hydrochloric acid² have both been shown to increase bronchial responsiveness in some asthmatic individuals. As soft drinks (pH about 3) are frequently served iced this could be a potential hazard for many individuals with asthma, particularly children.

The mechanism of this response is unclear but is likely to be due to stimulation of the upper gastrointestinal tract, although conditioning of the inspired air is a possibility. The study was designed to differentiate stimulation of the oropharynx and the oesophagus by assessing the airway response to orally retained and swallowed ice or hydrochloric acid; modification of the inspired air by the two methods should be similar. A test of bronchial responsiveness was included in the assessment as this has previously been shown to facilitate the detection of a positive response to oral challenge.¹⁻³

Methods

SUBJECTS

Twelve patients giving a history of asthma exacerbated

by ingestion of ice or acidic drinks were selected from the asthma clinics at Hammersmith and Ealing Hospitals. Eight were children (6-15 years) and four were adults (21-57 years). Eight had severe asthma treated with inhaled steroids. All four adults had symptoms that were difficult to control. All the subjects originated from the Indian subcontinent but all the children were born in Britain. Inhaled bronchodilators were stopped for six hours and sustained action theophylline and cromoglycate for at least 12 hours before testing.

ORAL CHALLENGE PROCEDURE

The subjects attended on three separate days. They were challenged with either ice or hydrochloric acid, according to their history. The active challenges of ice (80 ml) or hydrochloric acid (200 ml, 0.01N), selected according to the history, were retained in the mouth on one study day and swallowed on another. The orally retained ice was contained in a polythene bag and sucked until it had melted. The resulting cooled saliva was gargled and spat out. The orally retained hydrochloric acid was also gargled and spat out. The placebo challenges consisted of a drink of 80 or 200 ml of tap water as appropriate. The challenges were administered in random order for each subject by a third party. The hydrochloric acid and corresponding placebo were artificially sweetened with five

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drops of saccharine solution and the swallowed active and placebo drinks, given double blind, were indistinguishable. The investigators were unaware which type of challenge had been given.

ASSESSMENT OF BRONCHIAL RESPONSIVENESS

On arrival in the laboratory on each study day the subjects rested for 10 minutes before measurement of FEV₁ (Vitalograph). This was then repeated at five minute intervals until a steady baseline was reached. A control histamine challenge test was performed by the method standardised by Cockcroft *et al.*⁴ Doubling concentrations of histamine solution (0.03–16 g/l) were inhaled from a Wright's nebuliser until at least a 20% fall in FEV₁ had occurred, to give the PC₂₀ value. Thirty and 90 seconds after inhalation of each concentration of histamine the FEV₁ was measured and the better of two measurements was accepted. An hour was allowed for recovery after completion of the control histamine test and the FEV₁ was then measured again, before oral challenge and 5, 10, 15, 30, 60, and 90 minutes afterwards. A second histamine test was then performed with the same set of histamine solutions and the same nebuliser. PC₂₀ was calculated by interpolation of the last two points on the dose-response curve.

STATISTICAL ANALYSIS

Analysis of variance was used to assess statistical differences between groups, allowing for differences between patients. To assess the significance of individual responses the 95% confidence intervals for changes in FEV₁ and PC₂₀ that occurred after placebo challenge were calculated. For PC₂₀, log_e transformation was used for all statistical analysis. The 95% confidence interval for change in PC₂₀ after placebo was calculated from the standard deviation of the 2nd:1st PC₂₀ ratio followed by antilog_e conversion.

Results

Twelve subjects completed the study and one subject was studied twice, with both ice and acid. In three there was less than a 10% fall in FEV₁ and no significant change in histamine PC₂₀ after oral challenge on any of the three study days. As an airway response to ingested ice or acid had not been demonstrated, these three subjects were excluded from further analyses. In six subjects a response was demonstrated after challenge with ice and in four after acid. Analysis of variance showed no difference in response between those subjects challenged with ice and those challenged with acid on the three study days. The 10 results have therefore been combined for assessment of mean changes in FEV₁ after challenge

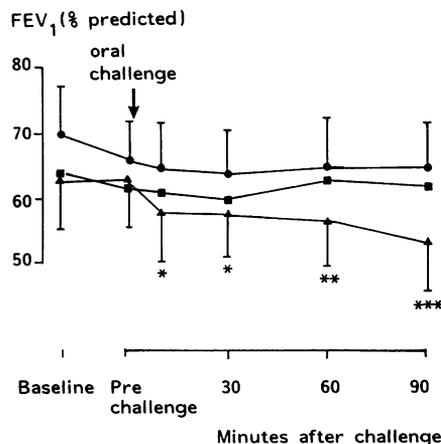


Fig 1 Results of ice and hydrochloric acid challenge combined (n = 10) to show the effect on mean (SE) FEV₁. ● Placebo; ■ orally retained challenge; ▲ swallowed challenge.

on each study day (fig 1). To calculate the 95% confidence intervals for change in FEV₁ and PC₂₀ after active challenge we used the mean results of the 10 subjects on the placebo study days.

There were no significant mean differences in baseline FEV₁ or control PC₂₀ between the three study days. After placebo or orally retained ice or acid mean FEV₁ and PC₂₀ did not differ significantly from

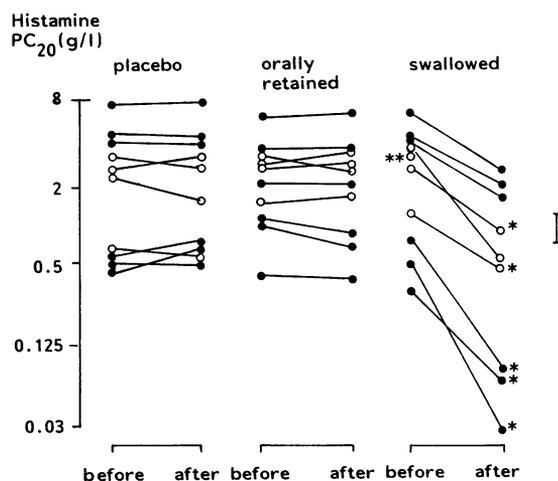


Fig 2 Individual histamine PC₂₀ values (concentrations causing at least a 20% fall in FEV₁) before and after challenge with ice (●) and hydrochloric acid (○), orally retained and swallowed and corresponding placebos. The bar shows 95% confidence interval of changes in PC₂₀ after placebo challenge. **No post hydrochloric acid histamine PC₂₀. *FEV₁ fell > 10%.

control values obtained before oral challenge. After the swallowed active challenges, however, there was a small but significant fall in mean FEV₁ at each time point (fig 1). The FEV₁ was significantly lower at 90 than at 10 minutes after challenge ($p < 0.02$). There was also a significant fall in mean PC₂₀ after the swallowed ice and acid ($p < 0.001$), but this was also associated with a significantly lower mean baseline FEV₁ before the second test ($p < 0.001$).

The 95% confidence interval for change in FEV₁ after placebo challenge was found to be $\pm 10\%$ and for change in PC₂₀ ± 0.75 histamine dilutions. No individual subject showed a greater than 10% fall in FEV₁ or a significant fall in PC₂₀ after the orally retained ice or acid. After the swallowed ice and acid six subjects showed 11–50% falls in FEV₁ but in only two was it over 20%. In one subject it was impossible to perform a histamine test because of the bronchoconstriction induced by ice ingestion. A significant fall in PC₂₀ was seen in all the remaining subjects (fig 2).

Discussion

We found that orally retained ice or dilute hydrochloric acid had no significant effect on airway function, whereas swallowed ice or acid provoked overt bronchoconstriction in some and an increase in bronchial responsiveness to nebulised histamine 90 minutes after ingestion in all subjects. This suggests that the oesophagus was the site of the event that initiated the sequence leading to airway narrowing or hyperresponsiveness.

For the group as a whole and for six individual subjects, after the ice or acid had been swallowed baseline FEV₁ was lower before the second histamine test, and this could be partly responsible for the finding of increased responsiveness.⁵ Even in the four subjects in whom the difference in baseline FEV₁ before the two histamine tests was less than 10%, there could have been an increase in peripheral airway resistance, undetected by the measurement of FEV₁. This could have resulted in an increase in central deposition of the histamine aerosol,⁶ with a consequent higher concentration on the central airway receptors and hence a reduction in PC₂₀. Indeed, aerosol penetrance has been suggested as a sensitive test for small airway function.⁷ Conventional tests of peripheral airways obstruction are controversial⁸ and would have been invalid in the presence of the large airways obstruction, which was present in many of the subjects in this study. In contrast, the measurement of histamine responsiveness is simple and reproducible even in the presence of poor lung function, and the PC₂₀ was used in this study simply to

facilitate the detection of an airway response to oral challenge.

The findings are unlikely to be spurious as both the FEV₁ and histamine PC₂₀ were shown to be reproducible after placebo and after the orally retained active challenge. The hydrochloric acid was given double blind and the active and placebo drinks were indistinguishable. The subjects would have been aware of swallowing ice and it remains a possibility, although unlikely, that the response was psychogenically determined. The FEV₁ was, however, lower 90 minutes than 10 minutes after challenge after both ice and acid, and previous experience has shown that the PC₂₀ is also lower 90 minutes than 30 minutes after ingestion of ice.¹ The pattern of the response makes a psychogenic mechanism unlikely.

This study shows that it was necessary for the ice and hydrochloric acid to be swallowed for an asthmatic response to occur. Inhalation of both cold air and acidic aerosols¹⁰ have been shown to cause bronchoconstriction. As conditioning of the inspired air during challenge by the hydrochloric acid and ice was likely to be similar whether the substances were swallowed or orally retained, cooling or acidification of the inspirate is unlikely to be the explanation.

The stomach already contains hydrochloric acid. Ingested ice, having been sucked and swallowed, would have neared body temperature by the time it reached the stomach, so the site of the stimulus is likely to be the oesophagus. There was no clinical evidence of any oesophageal dysfunction in any of the subjects. All the subjects, however, originated from the Indian subcontinent, so perhaps oesophagitis was more likely because of their highly spiced diet.

The mechanism whereby oesophageal stimulation can cause an airway response is not obvious. There is evidence from animal studies of both thermal¹¹ and acid sensitive¹² vagal receptors in the oesophagus. In dogs with induced oesophagitis oesophageal acidification with 0.1N hydrochloric acid resulted in bronchoconstriction, which could be abolished by vagal section.¹² Hydrochloric acid (0.1N) infused into the oesophagus has also been shown to induce bronchoconstriction in both adults^{13,14} and children¹⁵ with asthma in the presence of oesophagitis. In the same studies subjects without evidence of oesophagitis failed to show a pulmonary response to oesophageal acidification. It is clear from these and other studies that consider the role of gastro-oesophageal reflux in asthma that not all individuals with hyperresponsive airways respond to oesophageal stimulation, although some asthmatic subjects without symptoms referable to the upper gastrointestinal tract showed increased bronchial responsiveness after a drink of the hydrochloric acid as dilute as 0.001N² (pH 3.1).

Could a vagal reflex in certain susceptible subjects, particularly those with oesophageal mucosal damage, account for the results of this study? The similarity of the response to the two challenge substances would suggest a common pathway but the timing of the response, maximal at least 90 minutes after challenge, makes a simple reflex unlikely. Since bronchoconstriction after cooling of airways can result in a fall in oesophageal temperature¹⁶ during oesophageal cooling from ingestion of ice arguably the reverse could occur. In this study the bronchoconstriction following ice ingestion increased during the 90 minutes over which the FEV₁ was measured, a pattern not seen with cold air inhalation, which makes airway cooling an unlikely explanation. Cooling of the face¹⁷ and body^{18,19} have also been reported to produce bronchoconstriction, persisting for up to 15 minutes after return to normal temperature.¹⁹

Another possibility is non-immunologically provoked mediator release, similar to that seen with cold induced urticaria.²⁰ The timing of the response could suggest production of membrane derived mediators such as platelet activating factor or leukotrienes, both of which have been associated with increased bronchial responsiveness.^{21,22}

The subjects selected for this study all originated from the Indian subcontinent. The reason for this selection was to obtain a sample of patients with a high yield of positive responses to the oral challenges. Asians have previously been reported as more frequently giving a history of asthma induced by ice and fizzy drinks (pH 3.0) than non-Asians.²³ Although non-Asian subjects are known to respond to a drink of hydrochloric acid,² there is little published evidence to confirm that they show an asthmatic response to ingested ice. All the subjects in one previous study demonstrating ice induced asthma were Asian.¹ There is one case report²⁴ of ingestion of ice cream that caused nearly fatal asthma in a patient of unspecified ethnic origin, and early references to ice ingestion causing wheeze as part of a syndrome of "physical allergy" probably refer to non-Asian patients.²⁵ Asians with asthma seem unlikely to be alone in this susceptibility.

This study has shown that oesophageal stimulation by ingestion of ice and acid can exacerbate asthma. The idea of the oesophagus as a potential site for bronchoconstrictive stimuli is consistent with the frequently reported association of gastro-oesophageal reflux and asthma.^{26,27} The actual mechanism, however, remains unclear.

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