

# Gastro-oesophageal reflux and childhood asthma: the acid test

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**ABSTRACT** The presence of gastro-oesophageal reflux was investigated in 18 children with moderate to severe asthma by overnight oesophageal pH monitoring. Appreciable reflux was found during sleep in eight; its relevance to nocturnal asthma was not clear. On another occasion the same children were challenged in a double blind fashion with a drink of dilute hydrochloric acid (0.001 N) and the response of the airways was monitored by peak flow measurements and by histamine challenge tests. There was a significant increase in mean histamine sensitivity ( $p = 0.001$ ) 90 minutes after the acid drink without any associated change in baseline peak flow rate. Eight children had a significant response to the acid drink, and a further three reacted to a more concentrated solution (0.01 N). In those asthmatic children in whom reflux is associated with a positive response to an acid drink (five out of 18 in the present study) it seems likely that reflux exacerbates nocturnal symptoms.

The association of gastro-oesophageal reflux and asthma has been recognised for many years.<sup>1-3</sup> A causal relationship between severe reflux and symptoms of asthma has been suggested because symptoms often improve after fundoplication in those with gross reflux.<sup>1,4</sup> More directly, in the presence of oesophagitis instillation of concentrated hydrochloric acid into the lower oesophagus has resulted in increased respiratory resistance.<sup>5</sup> Whether "silent" reflux (that is, reflux unassociated with epigastric or retrosternal pain) could be a contributory factor in asthma is more controversial. Several studies have shown that in asthmatic subjects "silent" reflux is neither more frequent nor of greater degree than is encountered in normal controls.<sup>6-8</sup> Furthermore, episodes of reflux have been found to occur without respiratory symptoms<sup>6</sup> or alteration in pulmonary function<sup>8</sup> in asthmatic subjects. The relevance of reflux in an individual asthmatic patient may be difficult to determine. On the one hand, frequent reflux can occur quite independently of asthma but, on the other, even a single episode of reflux might be sufficient to trigger an attack of asthma in a sensitive patient.

In previous studies we have found the histamine inhalation test for bronchial responsiveness to be a more sensitive method of demonstrating a respiratory response to ingested substances in susceptible asthmatic subjects than measurement of resting lung function.<sup>9-11</sup> The present study was designed to investigate the possibility that a drink of dilute hydrochloric acid, mimicking acid reflux into the oesophagus, could increase bronchial responsiveness without necessarily altering baseline lung function. This "acid test" would then be a simple method for assessing the effect of acid in the oesophagus and thus determine the relevance of reflux in individual patients with asthma.

We carried out two studies in a group of asthmatic children. Firstly, so that we could determine the degree of spontaneous acid reflux, the children underwent overnight oesophageal pH monitoring. Secondly, we measured their response to a drink of dilute hydrochloric acid double blind, by seeking a change in the level of airways obstruction and the degree of bronchial responsiveness to histamine.

## Methods

### SUBJECTS

Eighteen children with asthma were selected for study (table). All were atopic as defined by reaction to at least one allergen on skinprick testing. Five had

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Clinical data, peak expiratory flow rate (PEFR) and histamine reactivity ( $PC_{20}$ ) before and after a drink of hydrochloric acid (pH 3.1) and placebo and the result of oesophageal pH monitoring in 18 children with asthma (bold figures represent a significant fall)

Patient No	Age (y:m)	Sex	Drugs*	Clinical features†	Placebo				HCl (pH 3.1)				Oesophageal pH	
					Baseline PEFR (%)		Histamine $PC_{20}$ (g/l)		Baseline PEFR (%)		Histamine $PC_{20}$ (g/l)		Episodes pH <4 for >2 min	% of time asleep pH <4
					1	2	1	2	1	2	1	2		
1	8:9	F	T	N	88	90	1.00	1.20	92	90	0.52	0.38	+	18
2	10:1	F	P, I	S	100	106	1.45	1.25	69	76	2.00	1.8§	+	28
3	13:10	M	I, B	N, D	102	86	0.07	0.85	100	102	0.70	<b>0.06</b>	+	7
4	8:6	M	P, I, B	S	83	66	0.37	0.28	70	72	0.31	<b>0.03</b>	+	6
5	11:7	F	T	N, D	86	58	0.15	0.16	80	56	0.38	<b>0.10</b>	+	36
6	10:6	M	I, T†	N	84	74	0.13	0.14	86	66	0.17	<b>0.05</b>	-	<1
7	13:5	M	I, T	N, E	70	73	3.5	3.8	62	65	0.70	0.75	-	<1
8	10:4	F	I, T, B†	N	62	58	0.18	0.20	63	60	0.10	<b>0.02</b>	+	17
9	8:5	M	I, T	N	85	78	4.0	8.0	78	74	6.00	4.0	-	<1
10	6:6	F	T	N, D	85	83	4.0	4.0	69	85	0.39	0.29	-	<1
11	13:1	F	P, T, B†	S	68	72	0.26	0.13	58	67	0.20	<b>0.03</b>	-	<1
12	5:4	F	B	N, D	69	69	0.58	0.46	78	75	0.52	0.69	-	<1
13	13:6	M	I, B	S	92	88	0.40	0.36	98	95	0.74	1.13§	-	<1
14	9:2	M	C	D	64	68	0.67	0.32	62	60	1.30	<b>0.31</b>	-	<1
15	9:4	M	—	D	93	102	0.54	0.68	115	106	0.28	<b>0.09</b>	-	<1
16	12:7	F	P, C, T, B†	S	94	100	0.48	0.74	112	110	0.20	0.10	+	2
17	9:5	F	I, T†	N	72	56	1.80	2.00	72	84	1.5	1.0	+	2
18	13:0	F	T†	D	111	100	0.30	0.37	118	85	0.32	0.29§	-	<1

\*B—sustained release  $\beta$  agonist; T—sustained release theophylline; C—sodium cromoglycate; I—inhaled steroids; P—alternate day steroids.

†Tested while having treatment.

‡N—nocturnal; S—severe; D—drink related asthma; E—epigastric pain, "heartburn."

§Responded to HCl pH 1.9.

severe asthma with intractable symptoms. Nocturnal asthma was a notable feature in 10 children and three were selected on the basis of a history of exacerbations of symptoms after proprietary drinks. The latter symptom was also noticed by four of the other children. Only one child (subject 7) complained of symptoms compatible with oesophagitis.

#### THE "ACID" TEST

Where possible the morning doses of theophylline, sodium cromoglycate, or oral  $\beta$  agonists were stopped. No inhaled  $\beta$  agonists were taken less than six hours before the study. Because most of the children had severe nocturnal symptoms without treatment, they were unable to stop slow release night time medication. Six children were also unable to manage without sustained release  $\beta$  agonists or theophylline during the day, but care was taken to ensure that all medication was taken at exactly the same time before each study. Since our aim was to detect change in bronchial responsiveness and not its absolute level, we reasoned that prolonged action bronchodilator drugs should be acceptable under the double blind conditions of the acid test.

The children attended the laboratory on at least two days. On each day, after we had established a steady baseline in peak expiratory flow rate (PEFR;

Wright peak flow meter), a control histamine inhalation test was performed according to the two minute tidal breathing method of Cockcroft and co-workers.<sup>12</sup> Normal saline and then doubling concentrations of histamine (0.03–16 g/l) were given by Wright nebuliser and the response to each inhalation was measured by serial PEFR measurements, the best of three being accepted. Thirty minutes after the end of the histamine test PEFR was again recorded before a 200 ml drink of either dilute hydrochloric acid (0.001 N, pH 3.1) or water. The drinks, which were artificially sweetened with saccharin and indistinguishable, were given in a double blind randomised fashion. PEFR measurements were repeated 5, 10, 15, 30, 60, and 90 minutes later, when a second histamine test was performed with the same nebuliser.

The histamine  $PC_{20}$  the concentration of histamine which produced a 20% fall from the baseline PEFR, was calculated from the dose-response curve by interpolation. Mean differences in histamine  $PC_{20}$  and PEFR were assessed by a paired *t* test, after logarithmic transformation of the  $PC_{20}$ . A significant individual response to hydrochloric acid was defined as one that exceeded the 95% confidence limit of the within subject variation in PEFR and  $PC_{20}$  that occurred after water (placebo).

The children in whom no response to the hydrochloric acid drink (pH 3.1) could be detected were retested on a third day with the same protocol but hydrochloric acid 0.01 N (pH 1.9) was given.

#### OESOPHAGEAL pH MONITORING

Overnight oesophageal pH monitoring was carried out at either the child's house or in hospital, according to the parents' wish. After calibration with standard buffered solutions (pH 7.0 and 4.0) the miniature pH probe (Microelectrodes Inc) was inserted through the anaesthetised nose to the level of the mid oesophagus. The distance was estimated from a formula relating oesophageal length to height.<sup>13</sup> The probe was attached to a battery operated pH meter (Data Scientific PTI 55) and chart recorder (Tekman) running at 2 mm/min. The children were encouraged to eat, drink, and sleep normally and a detailed record of ingested items and activities was kept. Medication was continued as usual.

Only traces obtained during sleep were analysed. A fall in oesophageal pH to less than 4 for over two minutes was taken as evidence of acid reflux. This arbitrary definition was based on the duration of fall in pH that occurred after an acidic drink. The proportion of sleeping time during which oesophageal pH was less than 4 was also calculated.

#### Results

##### ASSESSMENT OF GASTRO-OESOPHAGEAL REFLUX

Eight children had at least one period when the

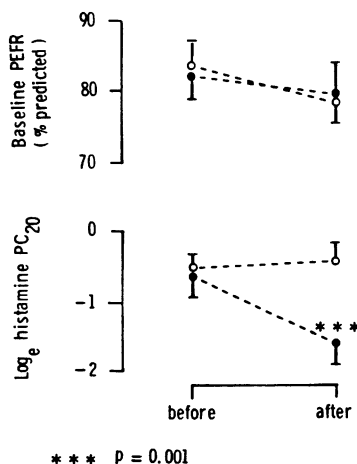


Fig 1 Mean peak expiratory flow (PEFR) and histamine PC<sub>20</sub> in 18 children with asthma before and 90 minutes after a drink of placebo (O) and hydrochloric acid pH 3.1 (●). Bars represent standard errors.

oesophageal pH fell below 4 for at least two minutes during sleep (table). So by our definition reflux was present. A similar fall in pH was seen for shorter periods on all the recordings on at least one occasion.

#### THE "ACID" TEST

There was no significant difference in mean baseline PEFR or control PC<sub>20</sub> between the two study days (fig 1). There was no significant change in mean PEFR or PC<sub>20</sub> 90 minutes after placebo; but 90 minutes after the hydrochloric acid (pH 3.1), although the mean PEFR did not change, the PC<sub>20</sub> was significantly lower (p = 0.001; fig 1).

One child (subject 5) showed a 32% drop in PEFR 15 minutes after hydrochloric acid. She also, however, showed a progressive fall in PEFR during the study period of the placebo day. In the others the variation in PEFR after both hydrochloric acid and placebo was within 20% of the value before the drink.

The within subject coefficient of variation of PC<sub>20</sub> after placebo was 48% with a 95% confidence limit for changes in PC<sub>20</sub> after hydrochloric acid of ± one dilution. Eight children showed a fall in PC<sub>20</sub> of more than one dilution after hydrochloric acid (table). One child (subject 3) showed a considerable and inexplicable increase in PC<sub>20</sub> after placebo.

Ten children whose PC<sub>20</sub> was unaffected by the

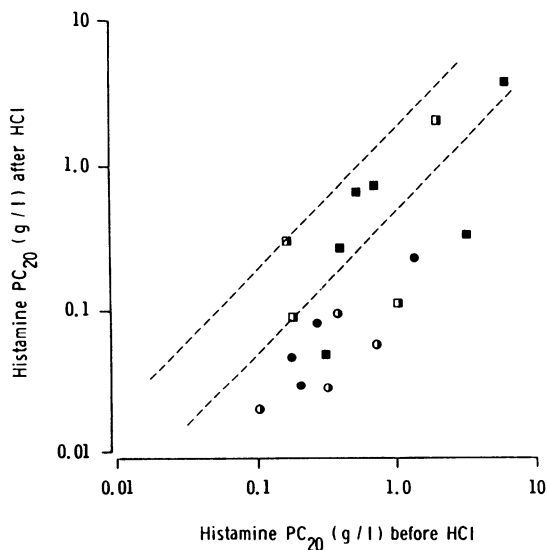


Fig 2 Individual histamine reactivity (PC<sub>20</sub>) in 18 children with asthma before and 90 minutes after a drink of hydrochloric acid (HCl). ----- denotes 95% confidence limit of change in PC<sub>20</sub> after placebo. ● HCl pH 3.1, no reflux; ◐ HCl pH 3.1 and reflux; ■ HCl 1.9, no reflux; ◑ HCl 1.9 and reflux.

dilute hydrochloric acid were retested with the more concentrated solution (pH 1.9, 0.01 N). A further three responded, two with a fall in PEFR of more than 20% as well as with a significant reduction in PC<sub>20</sub>. One responded with a fall in PC<sub>20</sub> alone.

#### ASSOCIATION OF REFLUX WITH A POSITIVE RESPONSE TO "ACID" TEST

Five children showed reflux and increased bronchial responsiveness after hydrochloric acid (table and fig 2). All had considerable nocturnal symptoms.

#### Discussion

Minor degrees of spontaneous acid reflux were seen in all of the children. With our arbitrary definition, reflux was present during sleep in eight of the 18 children. This is similar to the incidence previously found in asthmatic patients and normal controls.<sup>6,7</sup> In other studies an increase in reflux has been shown after meals<sup>8</sup> and with manoeuvres that increase intra-abdominal pressure.<sup>7,14</sup> "Silent" reflux has been shown to occur for up to 4% of the time in normal subjects without oesophagitis<sup>15</sup> and may become more pronounced in the presence of the lung hyperinflation and increased transdiaphragmatic pressure swings that occur in asthma. In the present study we are therefore likely to have underestimated overall frequency and degree of "silent" reflux which might be expected over a full 24 hour period.

Both theophylline<sup>16,17</sup> and  $\beta$  agonists<sup>17,18</sup> have been shown to reduce lower oesophageal sphincter tone and could thereby facilitate reflux. In the present study 13 of the children were monitored while having such treatment but no more reflux was noted in them than in five other children (table). Berquist and co-workers found that bronchodilator treatment in both asthmatic children and normal adults did not increase silent reflux.<sup>8</sup>

Apart from pulmonary aspiration, the relevance of reflux in asthma will depend on the airway response to the presence of acid in the oesophagus. A drink of dilute hydrochloric acid (pH 3.1, 0.001 N) significantly increased sensitivity to inhaled histamine in eight of the children and a further three responded to the more concentrated solution. A significant reduction in PC<sub>20</sub> was defined as greater than one histamine dilution, the 95% confidence limit of reproducibility set by placebo. The effect of treatment cannot be responsible, as all medication was given at the same time before each study day in this double blind assessment. Bronchodilators failed to protect four of the six children who were tested while receiving medication from the acid induced

increase in bronchial responsiveness. The increased responsiveness occurred without significant change in baseline PEFR. It could be argued that a more sensitive test might have detected small changes in lung function, but we have found that specific airways conductance may also be unchanged after an acid drink, despite a reduction in histamine PC<sub>20</sub> (unpublished observations).

The interval between the acid drink and histamine challenge was 90 minutes. This time was chosen because we have found this to be the time at which the maximum change in bronchial responsiveness occurs after ice challenge.<sup>11</sup> Partial recovery often occurs by 150 minutes (unpublished observations). Indeed, the pattern of increased bronchial responsiveness without significant change in baseline PEFR was also very similar to that reported after cola drinks<sup>9</sup> (pH 2.7) and ingestion of tartrazine capsules<sup>10</sup> as well as ice,<sup>11</sup> suggesting a similar mechanism. Other workers have shown that the more powerful stimulus of concentrated hydrochloric acid (0.1 N) instilled into the oesophagus in the presence of oesophagitis can induce an immediate increase in respiratory resistance<sup>5</sup> and alteration in respiratory inductance<sup>19</sup> in asthmatic subjects. Two of our patients did develop measurable airways obstruction, but only after a stronger concentration of acid.

A vagal reflex seems at first to be the most likely explanation. In dogs with induced oesophagitis an increase in pulmonary resistance after intra-oesophageal instillation of 0.1 N hydrochloric acid was abolished by vagal section.<sup>20</sup> It is, however, difficult to explain a response detectable 90 minutes after the stimulus as the result of a simple neurological reflex. Although we have assumed that the site of action of a drink of hydrochloric acid is in the oesophagus, the oropharynx is also a possible site. The site of action cannot be determined from the present study, although preliminary work comparing the effect of gargled and swallowed hydrochloric acid suggests that the solution has to reach the oesophagus to alter responsiveness (unpublished observations).

In the present study three children responded to the more concentrated hydrochloric acid (0.01 N) but not the more dilute solution, suggesting a dose dependent response. In two of the children the response to the more concentrated acid was detectable with PEFR measurement, but again the fall in PEFR in both was maximal 90 minutes after acid, the longest time interval assessed. Berquist and co-workers have found reflux in asthmatic children without any associated alteration in FEV<sub>1</sub>.<sup>8</sup> They did not, however, look for a delayed response or for change in bronchial responsiveness. The results of

the present study suggest that spontaneous acid reflux during the night may exacerbate the effect of the many other factors associated with nocturnal asthma.<sup>21</sup> The airway response to acid in the oesophagus is, however, likely to vary with the size of the stimulus and the degree of underlying hyper-responsiveness. The latter is known to be increased at night<sup>22</sup> and varies greatly from day to day in children (unpublished observations), so reflux could at times result in measureable airflow obstruction in this group of children, particularly during the night.

We have found that many proprietary drinks have a pH in the region of 3 (cola 2.7, orange squash 2.7, lemonade 3.0, apple juice 3.3, blackcurrant juice 3.0), suggesting that those children who responded to the dilute hydrochloric acid (pH 3.1) could be at risk from ingested acidic drinks as well as acid reflux. In the study seven children gave a history of asthma exacerbated by various drinks. Five of them responded to the dilute hydrochloric acid, suggesting that in these children the low pH of the drink, as well as possible sensitivity to tartrazine or other additives, could be responsible for their drink related symptoms. In our experience most children with a history of drink related asthma originate from the Indian subcontinent.<sup>23</sup>

Five of the children in this study showed increased bronchial responsiveness after a drink of hydrochloric acid and also had considerable reflux (fig 2), and in these children at least reflux of acid into the oesophagus is likely to be relevant to their symptoms of asthma. Confirmation of this might be obtained by a clinical trial of an effective antacid regime. Fundoplication to reduce reflux has greatly benefited children with gross reflux in uncontrolled studies,<sup>14</sup> whereas magnesium hydroxide has failed.<sup>24</sup> Fourteen out of 20 adults with symptomatic reflux claimed a reduction in symptoms of asthma from a rather low dose of cimetidine at night.<sup>25</sup> In the present study we have shown that it may be necessary to increase gastric pH above 3.1 before an improvement in asthma is seen.

If we are correct in assuming that "silent" reflux may occur in anyone then all asthmatic individuals could be vulnerable to the effect of acid in the oesophagus. Like any other trigger of asthma, susceptibility to oesophageal acid is likely to be related to the severity of asthma. Thus in an acute attack of asthma, with the increased likelihood of reflux occurring, a vicious circle could develop. While this remains speculative, it is worth considering reflux as a factor in children with unresponsive asthma or severe nocturnal symptoms. As shown in this study, the susceptibility of any individual to oesophageal acid may be assessed easily, without the need for nasogastric tubes or complicated equipment for

measuring lung function, by means of the "acid test."

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