

Nebulised ipratropium bromide and sodium cromoglycate in the first two years of life

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SUMMARY In a double blind crossover trial, we compared sodium cromoglycate, ipratropium bromide, and water in 23 asthmatic children less than 2 years old (mean age 11.8 months). Each child received nebulised solutions containing 20 mg of sodium cromoglycate, 250 μ g of ipratropium bromide, or 2 ml water three times a day for three two month periods. Daily symptom scores did not show significant differences between the treatments but parental preferences indicated that both sodium cromoglycate and ipratropium bromide were superior to placebo. Sodium cromoglycate was prophylactic and was more likely to help the older patients. Ipratropium bromide produced an immediate clinical benefit and the response was not age dependent. We were unable to pick responders from non-responders on the basis of lung function tests performed on a routine outpatient basis. Both ipratropium bromide and sodium cromoglycate help some but not all asthmatic children aged less than 2 years.

Asthma is common but difficult to treat in the first two years of life. Salbutamol is ineffective in most children until they are at least 1 year old.¹ Previous work with the anticholinergic agent, ipratropium bromide, is more encouraging and indicates that about 40% of young asthmatic children have a significant response, as measured by a fall in airways resistance (Raw) of at least 15%.² The clinical role of ipratropium bromide has not, however, been established in this age group and the exact role of sodium cromoglycate is also unclear.³ Recent studies have included young children with asthma^{4,5} but they have not reported whether there is a minimum age at which children respond to sodium cromoglycate.

Anecdotal evidence indicates that only some young asthmatic children respond to ipratropium bromide or sodium cromoglycate. The administration of these drugs to children in the first few years of life requires a compressor and nebuliser, and since these are expensive and not readily available it is very important to find factors that enable us to pick responders from non-responders. This prompted a double blind study comparing nebulised solutions containing placebo, sodium cromoglycate, and ipratropium bromide.

Patients and methods

Altogether 23 children, 19 boys and four girls,

completed the study. Their average age on admission was 11.8 months (range 4.0-23.6 months). All had suffered from recurrent attacks of wheezing and were considered to have troublesome asthma by both their paediatrician and their parents. Twelve had a history of eczema and 14 had a first degree relative with asthma. Blood and skin tests of allergic status were not performed routinely. Ten of the children had previously been admitted to hospital with bronchiolitis. Apart from this we found no conditions such as neonatal ventilation or bronchopulmonary dysplasia that might influence their likelihood of wheezing.

During a two week 'run in' period each child received a nebulised solution containing 2 ml water three times a day via a Sandoz nebuliser and Nebupump compressor. The parents kept a diary card at home, recording cough and wheeze each day and night, as well as concomitant drug treatment. Each symptom was scored from 0 (no symptoms) to 3 (severe) so that the worst possible daily score was 12.

At the completion of the initial two week evaluation, we assessed lung function and response to water and ipratropium bromide. We sedated the children with 80-100 mg/kg chloral hydrate and measured thoracic gas volume (TGV), airways resistance (Raw), and specific conductance (sGaw) using total body plethysmography.⁶⁻⁸ After initial baseline values were recorded, each child inhaled a

nebulised solution containing 2 ml of water and the lung function assessment was repeated 15 minutes later. We then administered a 2 ml solution of 250 µg of ipratropium bromide. Final measurements were obtained a further 15 minutes later.

The principal part of the study was a double blind crossover trial comparing 2 ml nebulised solutions containing 20 mg sodium cromoglycate or 250 µg of ipratropium bromide with water. These were given three times a day, each for two months. The average ages of the children at the start of the three treatment periods were 14.4, 14.4, and 14.6 months respectively. Symptoms were recorded on diary cards, as in the two week run in period. The 23 children completed the study but three parents lost diary cards for one of the periods, so that we have complete symptom scores for only 20 children.

Fully informed parental consent was obtained for each child and the local ethical committee approved the project. Statistical analysis of lung function data was by paired *t* tests while other data were analysed by paired Wilcoxon and binomial tests. Diary cards were analysed using the last 50 days of each treatment period and the last 10 days of the run in period.

Results

The symptom scores for the 20 children with complete diary card records are shown in Table 1. The strong trends for fewer symptoms with sodium cromoglycate failed to reach statistical significance. One of the three children with incomplete records had a symptom score of 101 during the placebo period, compared with 0 on ipratropium bromide. The other two children had missing diary cards for the placebo period, which their mothers reported was very troublesome. Both these children had severe symptoms throughout the trial but their scores on ipratropium bromide (218 and 343) were less than on sodium cromoglycate (316 and 376 respectively). The usage of additional bronchodilators by the whole group was low. Approximately half the children received salbutamol at some stage during the study, in all cases during acute attacks of asthma.

All 23 children completed the trial and the indication of parental treatment preference and parental assessment of whether there was an immediate response to treatment is given (Table 2). As judged by parental preference, both sodium cromoglycate and ipratropium bromide were superior to placebo ($P < 0.05$) and ipratropium bromide had an immediate clinical benefit for some children ($P < 0.05$).

Lung function results are shown in Table 3. These

Table 1 *Diary card information for the last 50 days of each treatment period in the 20 children with completed records*

	Sodium cromoglycate	Water	Ipratropium bromide
<i>Wheeze score*</i>			
Mean	33	43	45
Range	(0-82)	(0-129)	(0-144)
<i>Cough score*</i>			
Mean	46	55	53
Range	(0-111)	(0-187)	(0-154)
<i>Total symptom score†</i>			
Mean	79	98	98
Range	(0-178)	(0-316)	(0-270)
<i>No of symptom free days</i>			
Mean	25	21	21
Range	(0-50)	(0-50)	(0-50)
<i>No of scores of 2 or 3‡</i>			
Mean	12	22	20
Range	(0-45)	(0-96)	(0-80)
<i>Total doses of other bronchodilators</i>			
Mean	7	5	9
Range	(0-48)	(0-26)	(0-57)
<i>Children with fewer symptoms than in run in period</i>	17	11	14

* Worst possible score 300; † worst possible score 600; ‡ worst possible total 200.

Table 2 *Parental assessments of preferred treatment and immediate response to treatment*

	Sodium cromoglycate	Water	Ipratropium bromide
Parent preferred treatment	8	1	8
Immediate beneficial effect	1	0	6

Table 3 *Lung function data at start of trial, including responses to 2 ml of nebulised water and 250 µg of ipratropium bromide (n=17)*

	Initial Mean (SD)	After water Mean (SD)	After ipratropium bromide Mean (SD)
TGV (percentage predicted for weight) ⁹	114 (26)	113 (24)	111 (21)
Raw (kPa 1 ⁻¹ s)	2.08 (1.08)	2.22 (1.29)	2.02 (0.99)
sGaw (kPa ⁻¹ s ⁻¹)	2.0 (0.7)	1.9 (0.8)	2.1 (0.8)

TGV=thoracic gas volume; Raw=airways resistance; sGaw=specific conductance.

were performed on a planned outpatient basis and not during acute attacks of asthma. We found no distinct subgroup who responded dramatically to ipratropium bromide but the presence of possible responders may have been obscured by the fact that many children had normal lung function initially.

The clinical responses of some individual patients convey information that is obscured by the group as a whole. A number of children had notable amelioration in symptoms as soon as they were provided with a nebuliser. In particular, one child had had 8 admissions to hospital in the previous four months but was virtually symptom free for the 6 months of the trial. Other children had wide fluctuations in symptoms during the period of observation and treatment had no obvious benefit. Ipratropium bromide had no prophylactic effect but 6 parents reported an immediate bronchodilator action and felt that this enabled them to manage acute attacks of wheezing effectively.

The benefit of sodium cromoglycate was also notable in a few children. Those who responded to sodium cromoglycate as judged by parental preference had an average age of 16.4 months (range 4.8–25.6 months) compared with an average age of 12.1 months (range 4.4–21.1 months) for those who responded to ipratropium bromide. The tendency for sodium cromoglycate to be more effective in older children seemed to be a factor for predicting who would respond.

Discussion

Sodium cromoglycate and ipratropium bromide helped some but not all asthmatic children aged less than 2 years. The observations of treatment with ipratropium bromide have important implications. Although regular treatment with ipratropium bromide did not confer any prophylactic benefit, some parents noted a consistent clinical response with decrease in breathlessness, cough, and wheeze for about three hours after treatment. Since the completion of the trial, three of these children have received ipratropium bromide on many occasions with consistent clinical response. This study was not designed to assess the relative merits of salbutamol and ipratropium bromide in childhood asthma but two of the children (both aged less than 1 year) who responded to ipratropium bromide failed on many occasions to respond clinically to nebulised salbutamol. These observations were made by the parents at home and by the medical and nursing staff during inpatient and outpatient attendances. The explanation for these findings is difficult but the observations confirm previous lung function studies performed in the convalescent phase of acute attacks of

asthma.^{1 2} Clearly only some very young children are helped but our data suggest that a therapeutic trial of ipratropium bromide is indicated in acute asthma in the first year of life.

Sodium cromoglycate is well established in the treatment of asthma in the preschool child and we found strong evidence that it was superior to placebo as judged by both day and night cough and wheeze, symptom free days, troublesome symptoms, parental preference, and improvement compared with the run in period. Although those who responded to sodium cromoglycate were usually older than the group as a whole, one child aged 5 months seemed to be helped.

We have no objective information on drug compliance from this study. Many parents found it very difficult, however, to administer nebulised treatment to young active children. Compliance is probably not a problem during acute episodes of wheezing where the motivation and benefit is immediate but may be a contributing factor to some of the non-responsiveness to sodium cromoglycate.

Most asthmatic children aged under 2 years have neither severe disease nor require the intensive and demanding treatment that a nebuliser and compressor pump involves. Nevertheless, there is a small group for whom most paediatricians regard themselves as therapeutically impotent. We believe that ipratropium bromide during acute attacks and sodium cromoglycate as prophylaxis are two alternatives that do help some but not all of these children.

We thank the parents, Professor D Hull, Drs P Barbor, D Johnston, and N Rutter who allowed us to study patients under their care. We also thank Fisons and Boehringer Ingelheim for supplying drugs and compressor pumps, and the Asthma Research Council and the Nestle Paediatric Travelling Fellowship (Australia) who provided financial support.

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Received 3 October 1983

British Paediatric Association

Annual meetings

1984	10-14 April	York University
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1987	7-11 April	York University