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Assessment of the clinical usefulness of nebulised ipratropium bromide in patients with chronic airflow limitation

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ABSTRACT The effect of adding nebulised ipratropium bromide to bronchodilator treatment was studied in 20 patients with severe chronic airflow limitation. Maintenance theophylline with or without a steroid preparation was continued and comparison made between placebo, nebulised salbutamol, and a combination of nebulised salbutamol and ipratropium. Although the mean FEV_1 values showed the combination to produce a small but significant increase in peak bronchodilatation over the effect of salbutamol alone, there were eight patients in whom no clinically useful improvement occurred. The remaining 12 patients did obtain clinically useful improvement in the magnitude or the duration of bronchodilatation (or both) as a result of the added ipratropium. The conclusion is that individual patients with chronic airflow limitation responded to the addition of nebulised ipratropium bromide in a variable way. Patients who could obtain additional benefit from ipratropium need to be identified by an appropriate reversibility study before its inclusion in their bronchodilator treatment.

Ipratropium bromide, a synthetic cholinergic antagonist derived from atropine, is thought to act by inhibiting cholinergic bronchomotor tone.[1] In patients with asthma its bronchodilator effect is usually less than that of β_2 adrenoreceptor agonists, whereas in patients with chronic airflow limitation ipratropium bromide appears to have a bronchodilator effect equivalent to or greater than these agents.[2,3] Its duration of action also appears to be longer.[4] Some studies[5,6] have found the combination of ipratropium with a β_2 agonist to result in greater magnitude or duration of bronchodilatation than with either drug alone, although this is not a universal finding.[7] Such studies suggest that ipratropium will probably be most useful in the management of patients with chronic airflow limitation. Although its precise role has not yet been established, the drug seems likely to be used as an addition to other bronchodilator treatment.

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In clinical practice it is difficult to extrapolate from studies describing mean changes to the expected response in an individual patient. Even though statistically significant, mean changes are often of small magnitude because of the inclusion of patients who have no significant improvement after the addition of ipratropium. This study was designed to investigate how individual patients with chronic airflow limitation respond to the addition of ipratropium bromide to their bronchodilator treatment and to assess how those gaining additional benefit can be identified.

Nebulised solutions were used to ensure optimal dosage and delivery of the agent to the lower respiratory tract. The dose of nebulised ipratropium was 0·5 mg, which on the evidence of data from asthmatic subjects[8] should produce a response close to maximal. Patients were maintained on their other usual bronchodilator drugs as they would have been in clinical practice.

Method

Twenty consecutive patients (16 men, and four women aged 45–81 years) attending the respiratory

unit for management of severe stable chronic airflow limitation were invited to take part in the study. All fulfilled the Medical Research Council criteria for chronic obstructive bronchitis.[9] Their FEV_1 ranged from 0·43 to 1·77 l (19–65% predicted) with a mean (SD) of 0·91 (0·36) l (33% (12%) predicted). The study was approved by the hospital ethics committee and informed consent was obtained from the participants. The patients had no cardiac or other respiratory disease. Asthma in particular was excluded by a combination of a negative past history, lack of spontaneous variability in airflow obstruction on a short term or seasonal basis, the persistence of severe obstruction even after maximal bronchodilator treatment, and (in some patients) a reduced gas transfer value (KCO less than 75% predicted in 14 of the 20 patients). All had been cigarette smokers but none was smoking at the time of the study. All patients were receiving a theophylline preparation, with therapeutic blood concentration, and a sympathomimetic aerosol, and some were having a corticosteroid preparation. The sympathomimetic agents were withdrawn at least 10 hours before each study but other treatments were maintained.

The study was double blind and radomised and conducted on three separate days commencing at the same time each morning. The test solutions used for the three days were as follows: (1) normal saline (3 ml); (2) salbutamol 5 mg (1 ml of 0·5% solution) and normal saline (2 ml); (3) salbutamol 5 mg and ipratropium 0·5 mg (2 ml of 0·025% solution). All test solutions were administered via an Inspiron nebuliser with a gas flow of 6 litres per minute. FEV_1 and vital capacity (VC) were measured with a bellows spirometer (Vitalograph), the best of three measurements being recorded. Gas transfer (single breath carbon monoxide uptake) and arterial blood gas analysis were also performed before the study. After the baseline FEV_1 and VC had been obtained the nebulised solution was administered. Subsequent measurements were made at 15 minute intervals for the first hour and at 30 minute intervals for the next four hours. We also set out to discover the minimum number and timing of spirometric measurements necessary for ascertaining whether a particular patient obtained additional improvement when ipratropium was added to salbutamol. In the statistical analysis means were compared with *t* tests.

Results

The baseline FEV_1 for the individual patients did not vary by more than 15% for the three study days and there were no significant differences between the mean baseline FEV_1 values on the three days.

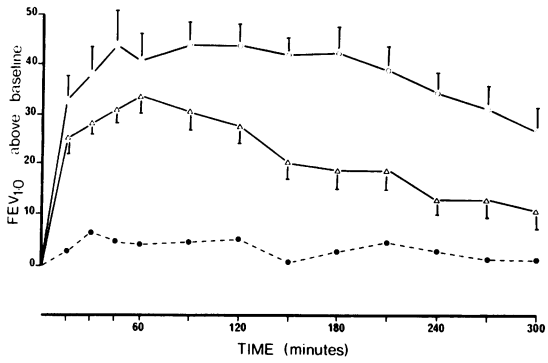

Fig 1 *Percentage increase in FEV_1 above baseline in 20 patients after administration of nebulised solutions (means and standard errors). O——O (top curve) ipratropium and salbutamol; △——△ salbutamol; ●——● placebo.*

No side effects were noted during the study.

The mean data for each study day are depicted in figure 1. The percentage increase in FEV_1 above baseline was significantly greater after salbutamol and also after the combination of salbutamol with ipratropium than after placebo at all times. The FEV_1 percentage improvement was greater after the combination than after salbutamol alone and reached significance ($p < 0·05$) for all time periods except 15 and 60 minutes. In absolute terms, however, this improvement in mean values after the combination of ipratropium and salbutamol compared with the mean values after salbutamol alone was not great; for example, the mean improvement over the corresponding salbutamol value due to the added ipratropium was 120 ml at 45 minutes, reaching a maximum of 210 ml at 180 minutes.

When individual responses were studied, the patients fell into three clearly definable groups in terms of the additional improvement obtained when ipratropium was given with salbutamol. An improvement with the combination treatment was defined as an increase in FEV_1 of at least 20% of the baseline value sustained for at least 30 minutes (that is, seen in two measurements 30 minutes apart) over and above the response obtained with salbutamol alone. Patients classified as "early improvers" showed such a difference in the first two hours of the study, while those defined as "late improvers" showed an additional response to the combination only after the first two hours. "Non-improvers" failed to show any such difference. On the basis of this classification six patients were early improvers, six late improvers, and eight non-improvers. For the early improvers (fig 2) the magnitude of the response with the combination of ipratropium and

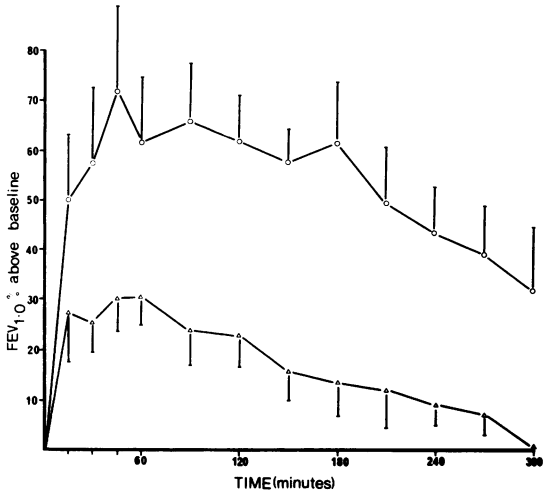

Fig 2 *Early improvers: percentage increase in FEV_1 above baseline for six patients (means and standard errors) (means significantly different from 30 to 300 minutes inclusive; $p < 0.05$). O——O ipratropium and salbutamol; △——△ salbutamol.*

salbutamol was about double that with salbutamol alone and the duration of improvement was significantly prolonged. This improvement was significant ($p < 0.05$) from 30 minutes to five hours. In absolute terms this mean augmented response above the salbutamol value was, for example, 312 ml at 90 minutes. In the late improvers (fig 3) the augmented response to the combined drugs was significantly greater than the response to salbutamol alone in all measurements made after two hours ($p < 0.02$). At 240 minutes, for example, this mean augmented response above the salbutamol value was 230 ml. For the non-improvers (fig 4) there was

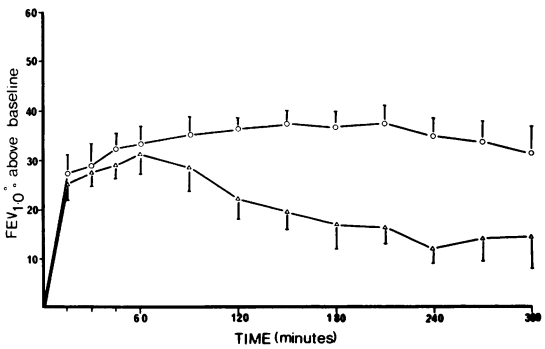

Fig 3 *Late improvers: percentage increase in FEV_1 above baseline for six patients (means and standard errors) (means significantly different from 120 to 300 minutes inclusive; $p < 0.02$). O——O ipratropium and salbutamol; △——△ salbutamol.*

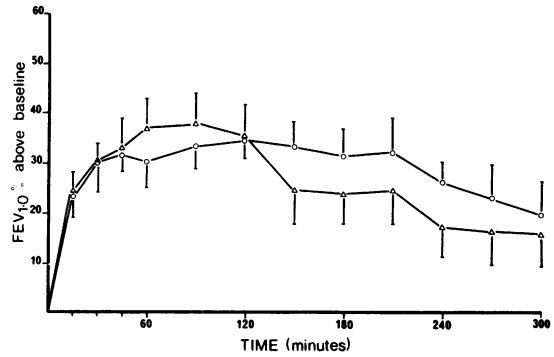

Fig 4 *Non-improvers: percentage increase in FEV_1 above baseline for eight patients (means and standard errors) (means not significantly different at any time). O——O ipratropium and salbutamol; △——△ salbutamol.*

no significant difference between the two curves at any time.

The vital capacity measurements, which were made at all time intervals, were less discriminating than the FEV_1 values and did not alter the division of patients into the above groups. The three groups of patients were compared according to their baseline lung function measurements to ascertain whether any of these indices was associated with a particular response. There were no significant differences between the groups of improvers and non-improvers in terms of age, baseline FEV_1, vital capacity, gas transfer, or ideal alveolar-arterial oxygen gradient. The maximum bronchodilator response to salbutamol was also not significantly different between either group of improvers and the non-improvers.

Each individual's response to the test solutions was examined to determine the minimum number of spirometric measurements necessary to separate early and late improvers from non-improvers.

It was necessary to measure the response to nebulised salbutamol alone for four hours and on a second day to ipratropium and salbutamol together for up to four hours. This procedure could be shortened only when the patient showed an increase in FEV_1 of at least 20% of the baseline value over and above the response obtained with salbutamol alone.

Discussion

In recent years there has been renewed interest in the use of anticholinergic bronchodilator agents, particularly since ipratropium has become available. This agent has a favourable ratio of bronchodilator action to extrabronchial side effects, even with high doses of nebulised solution,[8] and contrasts with the dose limiting side effects of atropinic drugs used

previously.[10] The addition of ipratropium to other bronchodilator treatment is logical because of its pharmacologically separate mode of action in blocking vagally mediated bronchomotor tone, a phenomenon also seen in normal subjects.[11]

The principal finding of the present study was that 2 ml of nebulised ipratropium bromide solution (0·5 mg) is a useful addition to bronchodilator treatment in some patients with chronic airflow limitation. So far as we are aware, the effects of combined nebulised solutions of ipratropium bromide and salbutamol have not previously been reported in such patients, nor have the responses been considered separately according to whether or not the addition of ipratropium was beneficial. Previous studies using metered aerosols of ipratropium combined with a sympathomimetic agent have produced differing results. Petrie and Palmer[7] and Leitch *et al*[12] found no additional benefit from the combination of ipratropium and salbutamol. On the other hand, Marlin *et al*[13] found that ipratropium combined with fenoterol did produce augmented bronchodilatation. Douglas *et al*[5] using a sequential design found the combination of ipratropium and salbutamol superior to either agent alone. Lightbody *et al*[14] compared consecutive three day periods of treatment and recorded similar conclusions.

The mean results from the present study are in accord with these latter observations, in that the response to the combination was significantly greater than the response to salbutamol alone for all measurements except those at 15 and 60 minutes. The peak improvement in the mean FEV_1 due to the ipratropium was, however, only 120 ml—a volume of doubtful clinical significance. The maximum mean improvement above the salbutamol value, apparent at 180 minutes, was 210 ml, a volume more likely to be clinically important. Hence these mean data suggest that the combination of salbutamol and ipratropium, while producing only a small improvement in peak response, may usefully prolong the bronchodilatation produced by salbutamol alone.

Patients were separated on the basis of whether or not they achieved a sustained increase in FEV_1 of at least 20% more than the baseline value with the addition of ipratropium over and above that achieved with salbutamol alone. The mean FEV_1 response for the six late improvers approximated to that of the group mean response—that is, although the peak response of these patients was not increased by the added ipratropium, the duration of the response was significantly prolonged. The early improvers, however, also had a much greater peak bronchodilatation than was apparent in the mean peak values for the 20 patients. This improved bronchodilatation was sustained for the five hours of the study. Thus it identified a previously unrecognised group of patients who obtained the greatest improvement from the addition of nebulised ipratropium to their bronchodilator treatment.

In the present study 60% of the patients had a beneficial response according to the defined criteria. Although this proportion may not strictly apply to other similar populations of patients all are likely to include individuals who obtain clinically useful benefit from the addition of ipratropium. This study also identified patients who received no such additional benefit. Their recognition is equally important since the addition of a non-effective agent could result in reduced compliance with effective medications—quite apart from the greater cost. On the basis of the lung function indices studied it was not possible to predict a beneficial response in individual patients. Hence spirometric measurements were necessary to distinguish between patients obtaining benefit from the ipratropium from those who did not.

It is therefore recommended that a trial of the addition of ipratropium to other bronchodilator treatment should be performed. On the first day the response to the sympathomimetic agent alone needs to be measured for four hours. On a second day, after ipratropium has been added, measurements should also be made for up to four hours. The trial may be terminated earlier if significant improvement above the corresponding sympathomimetic value is obtained. The recently reported possible adverse effect of increasing bronchoconstriction in occasional patients after the administration of ipratropium[15] should also become apparent during such a trial.

In summary, this study has shown that when nebulised ipratropium was added to nebulised salbutamol the combination achieved greater bronchodilatation than salbutamol alone. Patients could be separated on the basis of whether or not they achieved clinically significant benefit from the added ipratropium. Characterisation of the patients' individual responses to ipratropium by means of a reversibility study is recommended before treatment with this agent is started.

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