Nebulized Ipratropium in the Treatment of Acute Asthma*

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The efficacy of ipratropium and salbutamol was determined in 117 patients with acute asthma who presented to an emergency department to determine whether the order of administration of the two agents affects the improvement in peak flow rates. Patients were given two nebulized treatments at an interval of one hour in a randomized, double-blind design. They received either 5 mg nebulized salbutamol followed by 0.5 mg ipratropium, ipratropium followed by salbutamol, or both drugs administered together followed by nebulized saline. Ipratropium was an effective bronchodilator when given as the first agent.

Simultaneous administration with salbutamol was as effective as sequential administration. At one hour after treatment, there was no difference in peak flow between the combination of drugs and either drug given alone. Ipratropium given after salbutamol was not superior to saline solution given after the combination of drugs. Our data do not suggest a substantial therapeutic effect from addition of ipratropium to salbutamol in the immediate treatment of acute asthma. (Chest 1990; 97:430-34)

PEFR = peak expiratory flow rate; AVC = area under curve

Following the introduction of the newer anticholinergic antimuscarinic agents,1,2 a number of studies have investigated the use of such drugs in the treatment of acute asthma. Ipratropium is the most widely used of these newer agents, and it has been the most widely investigated, although the number of studies supporting its use is small.3-9

Ipratropium has been shown to be an effective bronchodilator medication in acute asthma.3,6 Three studies have suggested that sequential use of both an adrenoceptor agonist and an antimuscarinic agent is superior to one agent given alone,3 although there was conflicting evidence as to whether salbutamol should be given first in the sequence6 or last.4

Interpretation of the reports which support sequential administration may be biased because two active bronchodilators were administered sequentially. The second agent may cause further bronchodilatation because of its improved lung penetration which results from the effect of the first drug. This problem of design was addressed by two studies in which a comparison was undertaken between beta-agonist followed by an antimuscarinic and the beta-agonist given twice.6,7 Both suggested sequential treatment with the different drugs was superior, but in one,8 the group of patients who received two doses of beta-agonist probably had more severe asthma than those who received sequential treatment.

The above reports comprised relatively small numbers of patients, ranging from 12 to 28 patients in each. There were two studies of larger numbers of patients. In one study, 40 patients were allocated to two treatments of either salbutamol alone, or salbutamol combined with ipratropium.4 There was no difference in peak flow between the two groups at four hours. In another study of 148 asthmatic patients from four centers, patients were randomly allocated to three treatment groups and received a single nebulized treatment containing either fenoterol alone, ipratropium alone, or fenoterol/ipratropium in combination. At 90 minutes after treatment, the combination was superior to either agent given alone.9

We have undertaken a study to confirm that ipratropium is an effective bronchodilator in acute asthma, and to examine whether ipratropium should be given before, with, or after salbutamol for maximal treatment benefit in this setting.

METHODS

All patients presenting to the Emergency Department of the Royal Perth Hospital with acute asthma were entered into the study. Acute asthma was defined as dyspnea and wheeze in known asthmatic patients with deterioration of their usual symptoms and/or pulmonary function or those with a compatible history and clinical findings subsequently demonstrated following the study to have asthma. The PEFR was taken as the best of three readings recorded by a Wright peak flow meter, the same instrument being used throughout the study.

Other inclusion criteria were age between 16 and 70 years and the ability to perform repeated peak flow readings. Exclusion criteria were glaucoma and prostatism. The study design was as follows:

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The patients received two nebulized treatments at an interval of one hour, with measurements of PEFR before, and 15 and 60 minutes after each treatment. The study was double-blind and randomized, and there were three treatment groups as follow:

(A) salbutamol (5 mg) followed by ipratropium (0.5 mg) at one hour.
(B) ipratropium followed by salbutamol at one hour.
(C) salbutamol with ipratropium, followed by isotonic saline solution (as placebo) after one hour.

The best of three peak flow readings was recorded by a Wright's peak flow meter, the same instrument being used in all patients. The aerosols were delivered from a nebulizer (Inspiron Mini-neb), driven by wall oxygen at a rate of 8 to 10 L/min. Each nebulized solution was made up to 4 ml with isotonic saline solution by the hospital pharmacy. If considered necessary by the attending physicians, patients were given intravenous aminophylline and hydrocortisone. Patients were withdrawn from the study if they became too sick to continue, or if they declined to receive the second nebulized treatment.

Statistical analysis was by paired Student's t-test for data within groups, and by unpaired Student's t-test for data between groups. The mean AUC was calculated for each group by trapezoidal integration, and the results compared by the unpaired Student's t-test.

Results

A total of 177 patients were entered into the study. Of those, 117 completed the study protocol in full, 40 in group A, 41 in group B, and 36 in group C. Sixty subjects were excluded for varying reasons. Forty one patients were either given the wrong trial preparation, or the full number of peak flow measurements were not made, documentation was inadequate, or peak flow readings showed unacceptable variation (>10 percent), suggesting poor technique. Eleven patients improved symptomatically following the first nebulization and refused to receive the second treatment (three from group A, four each from groups B and C). Eight were withdrawn by the attending physicians because of worsening asthma (three each from groups A and B, two from group C). One of this latter group was withdrawn after deteriorating acutely while receiving nebulized ipratropium.

Eleven patients received steroid supplements (group A, four; group B, two; group C, five). Six patients in group A received intravenous theophylline: three in group B, and seven in group C. One patient in group C was given intravenous salbutamol. No patient deteriorated to such a degree as to require artificial ventilation. None of the 177 patients who was entered subsequently died from asthma. Demographic data and initial peak flow readings of each group are shown in Table 1.

In group A, two patients deteriorated within 15 minutes of receiving salbutamol (greater than 10 percent fall in PEFR), one patient deteriorated within 15 minutes after ipratropium, and one after 60 minutes. Four patients failed to improve (but did not worsen) after administration of ipratropium. In group B, three patients deteriorated 15 minutes after administration of ipratropium. One patient deteriorated after instillation of nebulized saline solution.

There was a significant rise (p <0.001 unless stated) in PEFR after each nebulized treatment; in group A between A0 and A15, and A60 and A75; in group B between B0 and B15, B15 and B60 (p <0.025), and B60 and B75; in group C between C0 and C15, and between C60 and C75 (Fig 1 and 2). Figure 1 shows the absolute values of PEFR for each group plotted against time. There was no difference between the baseline values of the three groups. There were no significant differences in the AUCs for the three groups; the mean AUC for group A was 4721 L/min;
for group B, 4627 L/min; and for group C, 5015 L/min.

Figure 2 shows the results expressed as percentage rise of PEFR from baseline plotted against time. Ipratropium was effective when given as the initial treatment, but at one hour, there was no difference in peak flow between the combination of drugs and either drug given alone. The effect of ipratropium given after salbutamol was no different from that of saline solution given after the combination of drugs. Salbutamol had an equivalent bronchodilator effect whether it was given as the first or the second agent. At the end of the two-hour study period, there was no difference in PEFR between the groups.

Analysis did not differ when subjects who received intravenous aminophylline or intravenous salbutamol were excluded from the study. The absolute PEFR readings for this group are shown in Figure 3. The data expressed as percentage rise of PEFR from baseline plotted against time are shown for these subjects in Figure 4.

**DISCUSSION**

We have observed no difference produced in the improvement in PEFR over a 150-minute period in three groups of patients with acute asthma treated with inhaled salbutamol and ipratropium bromide given sequentially or in combination. It is possible that a type 2 error has occurred to account for the failure to show any difference between the groups. At 150 minutes, this study had a power of 80 percent to detect a difference of 63 L/min between the groups.

Figure 3. Peak expiratory flow rate (L/min) for each group plotted against time, excluding data from subjects who received intravenous aminophylline or salbutamol. Bars represent 1 SEM.

Figure 4. Peak expiratory flow rate expressed as percentage increase from baseline, plotted against time, and excluding data from subjects who received intravenous aminophylline or salbutamol. Bars represent 1 SEM.
in order to detect a 25 L/min difference at the 80 percent level, 170 patients in each group would be needed. These figures imply that, if such a difference exists between the treatment groups, the study would detect the difference eight times out of ten. This suggests one of three alternative explanations for our results; either the lack of difference in treatment effect between the three groups is a real phenomenon, or that if the study were to be repeated, the difference would be detected, or that the difference in treatments is too small to be detected with the numbers of subjects used.

This is the largest single-center study of its type of which we are aware and serves to highlight the difficulties inherent in performing such a study in order to detect relatively small treatment differences between groups. More importantly, if a difference does exist between these treatments, it is small, implying that one would need to treat many patients with both drugs in order to benefit a few.

Our results were not influenced by differential treatment with corticosteroids between the three groups. The clinical effect of steroids is not detectable earlier than three to six hours. Therefore, patients who received steroids at the commencement of our study would be unlikely to show any resulting effect within the period of study.

Ipratropium contains the preservatives benzalkonium and EDTA which have been shown to be bronchoconstrictor for a proportion of asthmatic patients. Our measured peak flow changes following ipratropium may reflect, in part, a bronchoconstrictor effect in the patients whom we studied. However, salbutamol also contains preservatives (oral communication, 1988, Glaxo Australia), which are present in similar concentration to those in ipratropium. Our data suggest that ipratropium is an effective bronchodilator when given as the first agent. It is difficult to hypothesize that the additives have a confounding effect selectively upon ipratropium but not salbutamol, and that the confounding effect occurs when the drug is given second but not when given first. In group C, who received ipratropium second, there is a fall in PEFR between 75 and 120 minutes. This may reflect the waning effect of salbutamol given at time 0, alone, or combined with lack of bronchodilator effect of ipratropium in these patients.

In agreement with previous studies, we have shown that ipratropium, when given alone as the first drug, is an effective bronchodilator. However, we have not found it to be superior to a placebo when placebo was administered following salbutamol and ipratropium in combination. We are unable to draw any definitive conclusion as to the place of ipratropium, since our study was not designed to compare ipratropium and placebo. The conflict between our findings and those of previous workers may relate to the different design of our study.

First, we report a substantially larger number of patients than previous studies, with the single exception of one report including patients from four centers. The remaining studies comprise substantially fewer (12 to 40 per study) patients than we report here.

Second, our trial design has a placebo in one arm of the study. This permits comparison between placebo, ipratropium, and salbutamol all given as the second nebulized preparation. A true control group, which received no treatment, is not ethical in an acute and potentially fatal medical condition. However, inclusion of a placebo as second treatment following an active treatment given first in one arm of a double-blind controlled study, considerably enhances the interpretation of our results. None of the previous reports had a placebo in its design.

Our study has shown no advantage in giving salbutamol and ipratropium separately rather than together. Clinical convenience may therefore dictate that the drugs should be given together. However, our results also suggest that the addition of ipratropium to salbutamol provides no additional benefit over a single agent given alone. Combination salbutamol/ipratropium was not superior to either agent alone at one hour. When given second, ipratropium was not superior to saline solution after combination. Similar conclusions were drawn from a study of eight nonacute asthmatic and bronchitic subjects. The change in PEFR which we found after saline solution is probably due to a continuing or "carry-over" effect of the salbutamol/ipratropium combination administered 60 minutes earlier, but we cannot exclude a direct effect of saline solution upon peak flow.

In contrast to an order effect of ipratropium, we found that salbutamol was equally effective whether given first or second in the sequence. There is an extensive literature supporting the use of salbutamol and other beta-agonists as the mainstay of bronchodilator therapy in the treatment of acute asthma, but the evidence in support of a role for ipratropium is scanty.

Our study was limited to the initial period of treatment of the acute episode of asthma. Our data covered a period of two hours and the additional time required for two volumes of 4 ml to be nebulized, totalling a maximum of approximately 150 minutes. We were unable to draw conclusions as to the effect of drug combinations beyond this period. However, the initial period when patients present to an Emergency Department represents the opportunity for most effective treatment. The response to therapy during this initial period may be a predictor for the subsequent response of the patient to treatment. Such initial bronchodilator response is often used to deter-
mine whether patients are subsequently admitted to hospital.\textsuperscript{15}

At present, the evidence for the routine use of ipratropium in addition to a beta-adrenoceptor agonist such as salbutamol is not strong. With one exception, studies have been performed on relatively small numbers of patients, and are not comparable to the very substantial body of evidence which supports the use of beta-agonists in acute asthma. In order to minimize the probability of type 2 errors when clinical studies are undertaken with small numbers of patients, it has been suggested that overview or meta-analysis of a number of studies should be performed.\textsuperscript{16} The authors of one report have combined their own data with that from some previous studies in this fashion.\textsuperscript{8} Their meta-analysis suggested an advantage from combined treatment. However, the deficiencies of meta-analysis are that data are aggregated which may not be directly comparable, since studies are performed in various centers and have different protocols for assessment and treatment. Because of such inherent difficulties with meta-analysis, any resulting conclusions are less robust than conclusions based upon data emanating from studies within single centers comprising large numbers of patients.

From review of the literature and from the data presented here, we suggest that the case for the routine use of ipratropium in the treatment of acute asthma remains unproven. Further clinical studies are necessary before ipratropium can be considered to have an established place in treatment of acute asthma. Such studies should be performed upon patients with acute asthma\textsuperscript{17} rather than basing conclusions upon studies of patients with asthma provoked, for example, by the withholding of routine therapy or by histamine inhalation. Such clinical studies should preferably be undertaken upon large numbers of patients with acute asthma, and the analysis of the resulting data may be enhanced by incorporation of a placebo within the trial design.

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