when muzolimine was given alone (cases 2, 5, 9, 12, and 20), and in cases of severe hypertension refractory to conventional antihypertensive agents, when muzolimine was added to the treatment already being given (cases 3, 4, 6, 7, 10, 11, 15, 16, 18, and 19).

Nephrotic syndrome, congestive heart failure (during the whole course of chronic renal failure), and the striking fall in urine output (in far-advanced chronic uraemia) are all responsible for salt retention and oedema requiring diuretic treatment. In all our uraemic patients with oedema administration of muzolimine resulted in complete resolution of the oedema; salt and water excretions increased considerably after adequate oral doses of the drug, despite creatinine clearances as low as 4 ml/min.

This favourable diuretic effect was obtained with single daily doses of the drug taken by mouth usually in the morning. No rebound phenomenon occurred at the end of the treatment. No adverse reactions were observed, apart from muscle cramps in three patients presumably secondary to excessive salt depletion.

The increase in potassium but not calcium excretion after administration of muzolimine appears particularly advantageous in patients with advanced uraemia because of their tendency to hyperkalaemia and hypocalcaemia. The significant fall in serum concentration of chloride observed at the end of treatment may reflect a primary effect of the drug on chloride reabsorption in Henle's loop.[10]

Renal function was not modified by muzolimine as shown by the constancy in creatinine clearance. Nevertheless, plasma concentrations of urea and uric acid were significantly increased, as is commonly observed after diuretic treatment in uraemic patients. This may be accounted for by a rise in tubular reabsorption of urea and uric acid secondary to the extracellular fluid volume contraction. A direct effect of the drug on tubular function, however, cannot be excluded.

These studies give convincing evidence that muzolimine is a potent diuretic extremely effective in treating salt retention in patients with advanced renal failure. It may even be preferable to other high-ceiling diuretics, such as frusemide: muzolimine given by mouth appeared to be effective in treating salt retention refractory to high intravenous doses of frusemide.

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Ipratropium bromide in acute asthma

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Abstract

Ipratropium bromide was given to patients admitted to hospital with acute asthma. A cumulative-dose-response technique in six patients showed that 500 μg given by nebuliser produced a maximal increase in peak expiratory flow rate. This dose of ipratropium bromide was included in a regimen in which it was given either two hours before or two hours after nebulised salbutamol to 22 patients. Ipratropium bromide given on admission was as effective as nebulised salbutamol. The two drugs in sequence produced greater bronchodilatation than either used alone, and the mean peak expiratory flow rate rose by 96% in four hours.

Thus giving ipratropium bromide in addition to salbutamol in severe asthma enhances the bronchodilator effect. Further studies are needed to determine whether the same effect may be obtained by giving two maximal doses of salbutamol two hours apart.

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Introduction

Inhaled atropine-like compounds are useful in treating airflow obstruction in chronic bronchitis and asthma. The latest preparation available is ipratropium bromide. It produces appreciable bronchodilatation but, on the whole, not as much as salbutamol. Ipratropium bromide and salbutamol in combination have an additive effect,[1] but some studies have failed to show this.[2 3] In these trials ipratropium bromide was given from a pressurised aerosol to patients with asthma, but not during an acute attack. Bronchodilators given from aerosol canisters are not particularly effective in severe asthma, but when given by nebuliser without positive pressure they are as effective as when given intravenously.[4 5] We studied the use of nebulised ipratropium bromide in acute asthma and compared it with nebulised salbutamol.

Patients and methods

We studied 28 patients (18 women and 10 men) aged 15-79 years admitted to hospital with an acute attack of asthma. Twenty-one were atopic. All had an arterial oxygen pressure of under 9·3 kPa (68 mm Hg) and a peak expiratory flow rate of less than 25% of the predicted value. Measurements of peak expiratory flow rate were made throughout with a Wright peak flow meter, the best of three readings being taken.

Selection of the dose of ipratropium bromide—A cumulative-dose

technique was used in six patients (mean age 48 years) to determine the lowest dose of ipratropium bromide that would produce a maximal response. The patients inhaled 250 μg in 4 ml of solution from a Hudson nebuliser with a mouthpiece. The nebuliser was driven by an air cylinder until all the solution was used. This took about 13 minutes. After an hour the peak expiratory flow rate was measured and a further 250 μg given. This procedure was repeated hourly until a maximal response was obtained.

Comparison of ipratropium bromide and salbutamol—Solutions of salbutamol and ipratropium bromide were nebulised in the same way and given to 22 patients (mean age 40 years). Both solutions were made up to 4 ml with 0·9% saline. Only the hospital pharmacist knew which treatment was given to the patients, who were allocated at random to one of two regimens. Eleven patients were given 500 μg ipratropium bromide on admission followed two hours later by 10 mg salbutamol. Next morning the drugs were given in reverse order starting at 9.00 am. The other 11 patients were given 10 mg salbutamol on admission followed after two hours by 500 μg of ipratropium bromide, and vice versa the next morning. The peak expiratory flow rate was measured one and two hours after each nebulisation. The maximal increase in peak expiratory flow rate after the first nebulisation was recorded as well as the difference between this and the maximal response to the second nebulisation. Further doses of nebulised salbutamol were given later on the first day if they were considered to be necessary but were not given within six hours of treatment on the second day. All the patients were given intravenous hydrocortisone by intermittent injection (6 mg/kg six hourly) during the trial, but no other bronchodilators were given. Asthmatics whose attacks were considered to be too severe were not included. All those who entered the trial completed it.

Results

Dose of ipratropium bromide producing maximal response—All six patients responded to the initial dose of ipratropium bromide, and the mean peak expiratory flow rate rose from 110 to 137 l/min (fig 1). One hour after the second dose of 250 μg the peak expiratory flow rate had increased to 154 l/min, a response of 40%. The third dose did not produce any further improvement, so a dose of 500 μg was used in the second part of the study. The mean pulse rate was initially 115 beats/min; after 750 μg it was 106 beats/min.

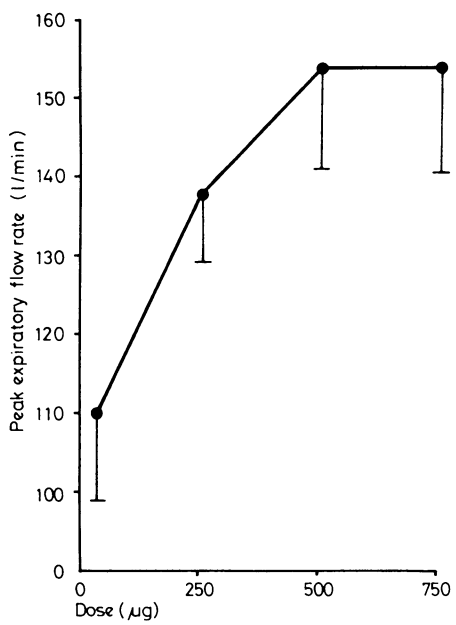

FIG 1—Dose-response curve for nebulised ipratropium bromide in six patients (mean ± SEM values).

Ipratropium bromide and salbutamol—Peak expiratory flow rate increased by over 15% in all 11 patients who received 500 μg ipratropium bromide on admission. Overall in this group the peak expiratory flow rate increased from 88 to 132·5 l/min, a mean response of 50% (range 18-132%) (fig 2). Of the 11 patients who received salbutamol first, two failed to respond by 15%. The mean response (49%), however, was the same as that obtained with ipratropium bromide, the peak expiratory flow rate rising from 103 to 153 l/min (range −5% to 170%). A second nebulisation two hours later on the day of admission (fig 2) produced a further increase. Salbutamol produced a greater increase than ipratropium bromide (43% compared with 23%), but the difference between them was not significant ($p = 0·1$, Student's t test). The total response in the two treatment groups on the day of admission was closely similar. On the second day (fig 2) the baseline values were higher. When given as the first nebulisation

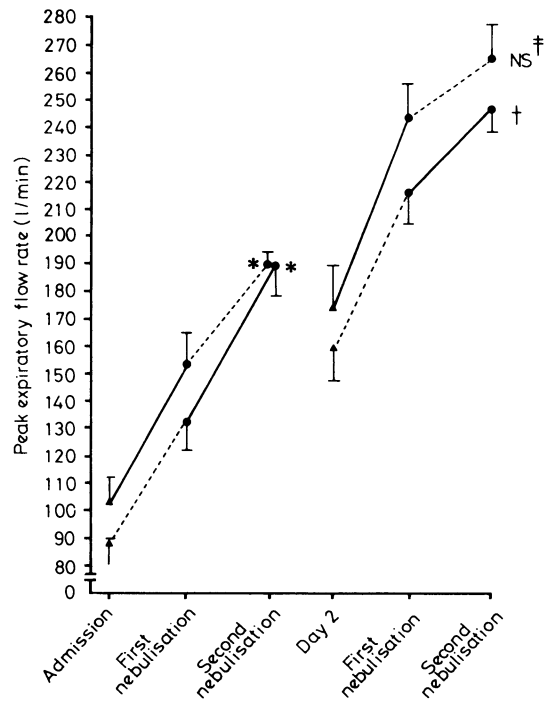

FIG 2—Changes in peak expiratory flow rate (mean ± SEM values) after administration of nebulised salbutamol and ipratropium bromide. ▲ indicates peak expiratory flow rate on admission and before treatment on next day. Responses to the two nebulisations are indicated by —— ● for salbutamol and - - - - ● for ipratropium bromide.

Significance of difference from result obtained after first nebulisation (paired t test): *$p < 0·001$; †$p < 0·01$; ‡$p = 0·08$.

both drugs produced an increase in the peak expiratory flow rate. Ipratropium bromide produced an improvement from 160 to 217 l/min (mean response 36%) and salbutamol an improvement from 174 to 244 l/min (mean response 40%). The second treatment on the second day produced smaller changes. Salbutamol given two hours after ipratropium bromide increased the peak expiratory flow rate from 217 to 248 l/min (mean response 14%), while ipratropium bromide produced an increase from 244 to 267 l/min (mean response 9%). The total response in both groups was again closely similar. Neither the age of the patient nor the type of asthma influenced the degree of improvement. There were no side effects or complications.

Discussion

In this study nebulised ipratropium bromide proved to be as effective as salbutamol in the initial treatment of patients with acute asthma. All the patients who received ipratropium bromide first showed a response of over 15% in peak expiratory flow rate, whereas two patients who received salbutamol first failed to do so. When ipratropium bromide was given two hours after salbutamol the response was not quite as good as the response to salbutamol after ipratropium bromide, but the difference between them was not statistically significant.

Salbutamol produces bronchodilatation by stimulating beta-

adrenergic receptors in bronchial muscle, and we used a dose that produces a maximal effect.[6 7] Ipratropium bromide works by blocking vagal reflexes. It is unlikely that the additional benefit obtained by using ipratropium bromide with salbutamol could have been achieved by using more beta-receptor stimulants. To verify this the study needs to be extended to compare the effect of two maximal doses of salbutamol given two hours apart with the effect of salbutamol and ipratropium bromide given sequentially two hours apart.

Some trials have failed to show any benefit from adding ipratropium bromide to salbutamol.[2 3] In mild asthma salbutamol may produce almost complete bronchodilatation, so that a second drug has no opportunity of showing its worth. The position may be different in more severe asthma, especially when the drugs are nebulised. Atropine methonitrate and salbutamol given in this way in fairly severe asthma are more effective than when given alone.[8] In our study ipratropium bromide and salbutamol were given two hours apart to permit an assessment of the contribution made by each. Even so, the mean peak expiratory flow rate rose by 96% in four hours. The patients might have benefited to the same extent more quickly if the drugs had been given closer together, and we are now studying this. Most of the improvement may be attributed to the bronchodilators because hydrocortisone, which was given to every patient, would have produced only a small increase in peak expiratory flow rate in four hours.[9]

We thank Boehringer Ingelheim for supplying the ipratropium bromide nebulising solution, the physiotherapists for their help, and the physicians at the hospital for allowing us to study their patients.

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Methotrexate treatment of squamous-cell head and neck cancers: dose-response evaluation

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Abstract

Seventy-two patients with advanced squamous-cell carcinomas of the head and neck were randomised to receive weekly intravenous methotrexate at doses of either 50 mg/m² (low dose), 500 mg/m² (medium dose), or 5 g/m² (high dose). Patients who failed to respond after four treatments at their initial dose were given four further treatments at the next higher dose. There were two complete responses and 21 partial responses to the initial dose—in 10 out of 22 patients given the high dose, seven out of 27 given the medium dose, and six out of 23 given the low dose. A further five out of 16 patients responded after crossing over to a higher dose. Toxicity was more severe with the high-dose regimen. Responders survived significantly longer than non-responders ($p < 0.05$), but there was no significant difference in durations of survival among the three treatment groups. Analysis of patients who completed the first four treatments indicated an improved response rate and duration of survival for the high-dose group.

Because of toxicity associated with high-dose methotrexate this treatment produces no overall greater benefit than low-dose regimens.

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Introduction

Methotrexate is the most widely used drug for advanced squamous-cell cancers of the head and neck.[1 2] Several workers have advocated the use of very high doses of methotrexate followed by folinic acid rescue in patients with tumours of the head and neck and other sites and claim greatly improved results.[3-7] This treatment, however, is often associated with severe toxicity and is very expensive.[6 8 9] Many methotrexate doses and schedules have been used but the importance of dosage has not been clearly resolved.[10 11]

We randomised patients with advanced head and neck cancers in a prospective study of the efficacy of three different weekly doses of methotrexate (50 mg/m², 500 mg/m², and 5 g/m²). All patients received identical pretreatment hydration and folinic acid rescue. A weekly treatment schedule was used in view of the reported superiority of this schedule over others.[6]

Patients and methods

Criteria for inclusion—From February 1978 to August 1979, 72 patients with advanced squamous-cell head and neck cancers were