

Inhalation therapy during acute asthma

The role of a combined steroid and beta-stimulant preparation

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Summary

A compound consisting of a β -stimulant, salbutamol (Ventolin; Allen & Hanburys) (100 μg /puff), and a steroid, beclomethasone dipropionate (Becotide; Allen & Hanburys) (50 μg /puff), was studied to test the hypothesis that the corticosteroid could enhance the bronchodilator properties of the β -stimulant during chronic asthma and simulated acute attacks (antigen challenge). Conventional doses (200 μg and 100 μg of salbutamol and beclomethasone respectively) were compared using a schedule which included a second administration 1 hour later. The results obtained on the baseline bronchial responsiveness of chronic asthmatics and during the delayed asthmatic response (simulated acute asthma) were similar. The compound was as effective as salbutamol alone but not more so. A significantly greater bronchodilator response was recorded in all patients after the second administration of both the compound and salbutamol alone. The practical advantages of having one rather than two inhalers are evident, but the appropriate application of this compound agent, probably in a prophylactic role, must be defined.

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The latest development in the treatment of acute prolonged asthma (APA) has been the addition of inhaled salbutamol (Ventolin; Allen & Hanburys) as an alternative or adjunct to intravenous bronchodilator therapy.^{1,2} The role of this agent, and possible alternative forms of inhalation therapy in conventional regimens during APA, have yet to be established. Drug trials conducted during APA are subject to a number of variables which make interpretation of the results extremely difficult. These include the degree of asthmatic obstruction, which in turn depends upon a variety of contributing factors, e.g. mucus plugs, infection, airways oedema and muscle spasm. In addition corticosteroids, an essential component of therapy, constitute a factor which influences the efficacy of bronchodilator agents.^{3,4}

This study was planned to circumvent these problems and to test a compound which contains salbutamol, a β -stimulant (100 μg /puff), and the steroid beclomethasone dipropionate (BDP) (Becotide; Allen & Hanburys) (50 μg /puff) under conditions of acute and chronic asthma. The compound has

been found to be as potent as the active components administered individually for control of clinical asthma in outpatients.⁵ Studies during APA with this agent have, however, not been reported. The delayed asthmatic response (DAR) which occurs 3 - 5 hours after inhalation challenge with antigen represents the closest model of APA which can be induced reproducibly with a minimum of uncontrolled variables.^{6,7} It differs from the early asthmatic response (EAR) in terms of response to inhaled β -stimulant and corticosteroid treatment. Corticosteroids inhaled before antigen challenge suppress DAR but not EAR.^{8,9} Beta-stimulants can prevent or suppress EAR, but doubt exists as to their bronchodilating properties during DAR. Hexoprenaline administered during DAR induces a temporary and incomplete reversal of airways obstruction, which lasts for less than an hour, and isoprenaline is similarly ineffective.⁹⁻¹¹

No studies have as yet been conducted to determine the effectiveness of corticosteroids alone or in combination with β -stimulants in reversing DAR. A study of this nature could be of value in determining how effective self-treatment with a nebulizer specifically containing a compound is in terminating APA. For this purpose the active agent salbutamol, BDP as well as salbutamol and the compound were administered separately during DAR to determine which agent or combination of agents would be most effective in terminating this phase of the asthmatic reaction. A similar protocol was followed in 5 stable chronic asthmatics. The degree and duration of bronchodilatation induced by the combinations of drugs was compared.

It has recently been reported that controlled administration of increasing amounts of salbutamol can determine the magnitude of bronchodilatation.¹² The possibility that conventionally prescribed doses may be too low for terminating an acute asthmatic attack therefore exists. A study of the influence of drug dosage administered by nebulizers in reversing DAR in naturally occurring asthma suggests that underusage rather than abuse prevails when patients attempt to reverse chronic or acute asthma with a commonly prescribed dose of bronchodilator agents. The new compound may have practical advantages for patients who require β -stimulant and corticosteroid agents for long-term prophylaxis. No evidence was found, however, that it is more effective than salbutamol alone for reversing the acute asthmatic response.

Patients and methods

A small group of asthmatic patients was included in one of two double-blind crossover studies. For both studies identical-looking inhalers were provided which delivered in each metered dose either: (i) 100 μg salbutamol with 50 μg BDP or (ii) 100 μg salbutamol or (iii) 50 μg BDP or (iv) placebo (freons and surfactant only).

On each occasion the patients were asked to take two inhalations from each of a pair of inhalers. The treatment schedule was the same for both studies and on 6 test days the patients received in random order the following inhalers: (i) placebo + placebo; (ii) combination + placebo; (iii) salbutamol

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+ BDP; (iv) salbutamol + placebo, repeated at 1 hour; (v) combination + placebo, repeated at 1 hour; and (vi) salbutamol + BDP, repeated at 1 hour.

Study 1

Chronic asthmatic patients were eligible to enter this study provided they had previously documented evidence of at least 20% variability of their airways obstruction. There were 3 males and 2 females, aged from 13 - 53 years, with atopic asthma as defined by history, skin tests and reversibility of airways obstruction. All were non-smokers, all required bronchodilator therapy, and 1 patient was receiving treatment with inhaled corticosteroids. Patients were instructed to cease their treatment 12 hours before study days.

After arriving at the laboratory on each occasion a baseline flow-volume curve was obtained. Patients performed this manoeuvre on a Collins dry seal spirometer until two identical curves were measured. The area below the flow-volume curve was determined electronically and was employed to determine the post-therapy and antigen challenge bronchial response. Care was taken to obtain the best standard baseline value for each individual on every study day and a mean variation of 16% between study days was recorded (the smallest individual variation being 7%, the largest 29%). The appropriate two inhalers were selected for each of the occasions, which were on successive days where possible and no further than 7-14 days apart. The flow-volume curve was repeated at 15 minutes and 1 hour after inhalation. According to the randomization code, on 3 test days the flow-volume curve was repeated at hourly intervals until 6 hours. On the other 3 test days a second dose (two puffs) from both inhalers was given 1 hour after the first treatment and the measurements repeated after a further 15 minutes, at 1 hour, and then at each hour until 8 hours (Fig. 1).

Study 2

Patients in this group were antigen challenged and the drugs administered during DAR. Atopic asthmatic patients who had previously been shown to have a dual asthmatic response following a specific antigen challenge were eligible to enter the study. The specific antigen had been identified by skin-testing and the challenge dose that produced both an immediate and late reaction had previously been identified for each patient. This proved to be house dust mite in 4 and grass pollen in 1 patient. Solutions of 1:5 000 - 1:10 000 for 2 - 4 minutes were employed for inhalation challenge. It was important to note that none of the patients was taking oral or inhaled corticosteroids during the week before each study day. Suitable patients were asked to attend the laboratory at 1 - 3-week intervals on 6 occasions, having withheld all asthma therapy for 12 hours before the start of each test day.

After arrival on each day, a baseline flow-volume curve was obtained and then the provocation test was performed. For each patient the concentration of antigen, rate of breathing and duration of nebulization were kept the same on all 6 occasions. A flow-volume curve was repeated initially at 15-minute intervals for the first hour and a half to identify the immediate response and then at hourly intervals.

The occurrence of DAR was considered established when, after recovery from the immediate response, the area under the flow-volume curve fell again at 2 time points. The appropriate two inhalers were then selected and administered during DAR by asking the patient to take two inhalations from both. On 3 test days, as determined by the randomization code, the flow-volume curve was then repeated after 15 minutes, 1, 2 and 3 hours. On the other 3 test days the flow-volume curve was repeated at 15 minutes and 1 hour, then a second dose was administered from both inhalers and the flow-volume curve repeated again after a further 15 minutes, 1, 2 and 3 hours (Fig. 2).

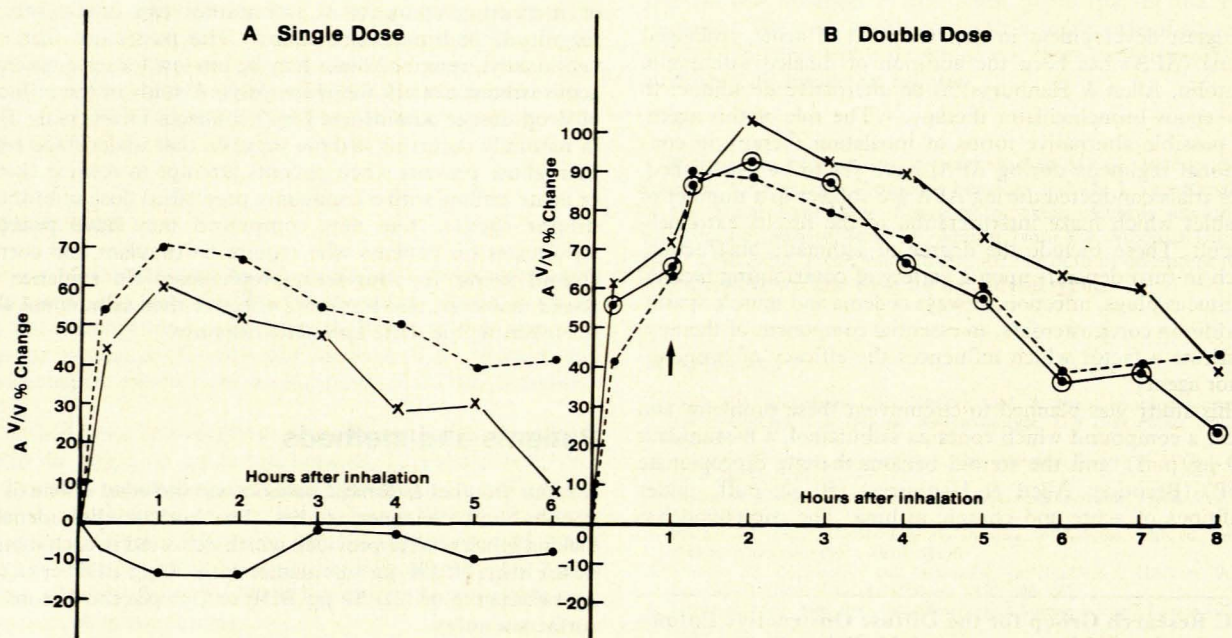


Fig. 1. The effect of different therapies on the bronchial response in chronic asthmatic patients. A — response to a single dose of the agent; and B — response to a second dose 1 hour after the first dose (indicated by arrow). Each point represents the change in the pre-challenge flow-volume curve value expressed as a percentage of the pre-challenge value (\bar{x} , $N = 5$), at various time points (● — ● placebo; x — x compound; ● - - - ● salbutamol and BDP; ⊙ — ⊙ salbutamol).

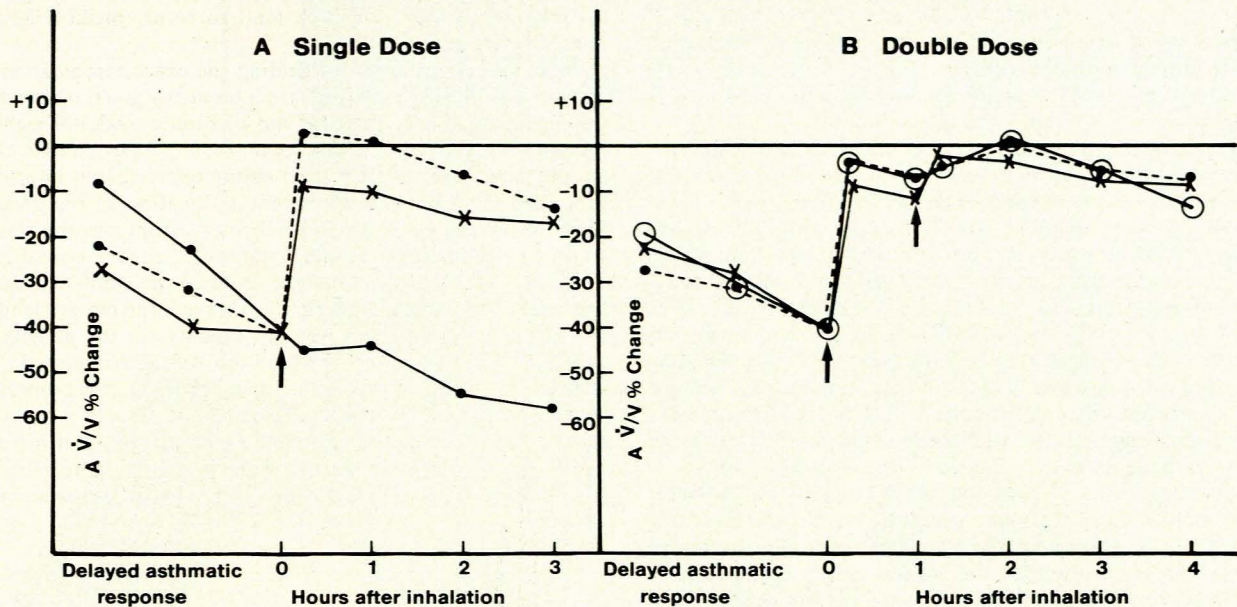


Fig. 2. The effect of different agents on the bronchial response to the delayed antigen-induced asthmatic reaction. For purposes of simplification the early asthmatic points were excluded and only two measurements at hourly intervals preceding drug administration are shown. A — response following a single dose of therapy and B — response following a second dose of therapy 1 hour after the first dose. Arrows indicate time points at which a single dose of therapy was administered. Each point represents the change in the pre-challenge flow-volume curve value expressed as a percentage of the pre-challenge value (\bar{x} , $N = 5$), at various time points (● — placebo; x — x compound; ● — salbutamol and BDP; ⊙ — salbutamol).

Results

Five asthmatic patients entered and completed each of the studies.

Study 1

The mean response curve for each test day has been plotted in Fig. 1. The mean predicted normal area under the flow-volume curve for the non-challenged chronic asthmatic group was 11,13 l²/s and a change of 15% (or 1,7 l²/s) in the area under the curve was considered significant. At 1 hour, all 5 active treatments produced a similar bronchodilator response which was always significantly greater than after the placebo (Fig. 1A and B). The placebo results were excluded from further statistical analysis of the data, since the pattern of response to placebo administration differed markedly from the response seen after treatment. In all cases, P_{MEAN} (placebo) was less than 1,0, while P_{MEAN} (active treatments) was greater than 1,0 at every point of observation. At 2 hours, both single-dose treatments were better than placebo and there was no difference in the response achieved with the combination inhaler or the two separate inhalers of salbutamol and BDP (Fig. 1A). At 6 hours there was no difference in the residual response between placebo and the combination inhaler. The effect of the two separate inhalers appeared to be more prolonged than that of the combination preparation at 6 hours, but this difference was not borne out by the overall response achieved by the two active treatments.

On the 3 days when a second dose was administered at 1 hour, there was no difference in the bronchodilator response induced by the three forms of active therapy during the subsequent 6-hour follow-up period (Fig. 1B); however, when comparing the single-dose and double-dose treatments, significantly greater bronchodilation was achieved at 2 and 3 hours on the days when a second dose was given ($P = 0,05$;

Wilcoxon matched-pair signed-rank test). This was true for all active preparations or combinations tested. As regards the residual response at 6 and 7 hours on the days after second doses had been given, the true treatments are equivalent. However, when comparing the area under the flow-volume curve at 6 hours on days when second doses were given with that of similar treatments at the same time on single-dose days, a trend was seen towards prolongation of bronchodilation by the second dose. This benefit was most marked with the combination inhaler (Fig. 1B).

Group 2

The mean values for the area under the flow-volume curves ranged from 5,04 to 6,66 before treatment, from 8,60 to 10,04 1 hour after active treatment and from 7,04 to 9,78 at the end of the study for the active treatment groups.

Comparison of the mean incremental response at 1 hour after treatment showed no significant differences between the 5 active treatments (Fig. 2A and B). At all time points after treatment the single-dose active treatments were better than placebo (Fig. 2A). At 3 time points after the second dose, a prolongation of effect was seen with all 3 treatments; this was most marked with the combination inhaler ($P = 0,05$). These values indicate that enhanced and prolonged bronchodilation was achieved during DAR by the double-dose regimens of all three active agents. No statistical difference was perceived between the results of double doses of the 3 active agents during DAR.

Discussion

The rationale for employing the compound in an acute asthmatic attack relates to the enhancing effect of corticosteroids on β -receptor sensitivity to administered β -stimulants. *In vitro* evidence has been found for higher levels of 3', 5'-cyclic

adenosine monophosphate, an inherent component of the β -receptor, being produced during corticosteroid administration.¹³ Self-treatment with the combination in an acceptable form could be of great value to asthmatics whose acute attacks occur at night or when far from medical assistance.

In a study in which inhalation preparations were employed for reversal of DAR, Joubert¹⁰ showed that inhaled corticosteroids enhanced the weak bronchodilating properties of hexoprenaline and theophylline. In the present study the efficacy of the combined agent during simulated acute asthma and chronic airways obstruction related to the bronchodilating action of salbutamol.

The age range of patients was wide but particular care was taken to exclude chronic bronchitis so that the bronchodilating effect indicated reversal of an asthmatic mechanism. Because of the amount of work involved specifically for repeated antigen challenge, results were obtained on a relatively small group of patients. This weakness in the study is offset by identical results in all subjects, which suggests that a larger study would lead to similar conclusions. No effect of the inhaled steroid agent on either the degree of responsiveness to the β -stimulant or duration thereof was clearly demonstrated. A possible reason for the findings of the present study relates to the potency of the β -stimulant.

Our results suggest that during the early phases of an acute asthmatic attack, β -receptor enhancement by corticosteroids does not play an important role if a highly effective agent such as salbutamol is used for bronchodilation. An important proviso for the success of β -stimulant inhalation therapy would be, in practice, that the patient should recognize early signs of onset of an acute attack of asthma. Prolonged periods of bronchoconstriction with subsequent mucous plug formation and oedema of the mucosa could substantially decrease the bronchodilator response to inhaled agents.

Patients frequently question their practitioners about the long-term safety of inhaled β -stimulant agents. Studies in which unexpected deaths related to alleged overdosage of isoproterenol are cited.¹⁴ Clear evidence was found in this study that in naturally occurring asthma as well as the antigen-induced DAR, salbutamol in the conventional dose of 200 μ g does not completely restore optimal airway patency. Improvement after a second dose of 200 μ g was recorded with either the salbutamol alone or the combined preparation. Spector and Gomez¹⁵ compared the effect of different doses of salbutamol and showed that a maximum dose of 680 μ g caused the greatest improvement in lung function in chronic asthmatics. No increase in side-effects was noted. This was borne out by the greater degree of bronchodilation achieved when a second dose of 200 μ g was administered at 1 hour either in the form of the compound or as individual sub-components of the combination preparation. Patients can therefore be safely advised to use their salbutamol nebulizers repeatedly at 10 - 15-minute intervals in double the conventional doses over a period of 60 - 90 minutes. If the symptoms of

airflow obstruction persist or tend to recur, medical advice should be sought.

As there exists no way of finding the exact combination of factors which cause airway obstruction at any given moment in any specific patient, an acute and a chronic model of asthma were employed. Clark and Anderson¹⁶ have shown that prophylactic use of BDP and salbutamol clearly improves long-term lung function of chronic asthmatics. In the present short-term study of a group of chronic asthmatics the therapeutic response was similar when nebulizers containing individual agents were employed or when the combined agent was inhaled as a single preparation. Although the bio-availability of the steroid component was not established, the activity of salbutamol in a combined preparation was demonstrated. We believe that a test of this agent for its prophylactic properties in chronic asthmatics should be carried out. It should prove to be as effective as the two separate agents, it would afford the asthmatic the practical advantage of using a single inhaler and might improve patient compliance with inhalation treatment.

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