Controlled Comparison of the Bronchodilator Effects of Three β -Adrenergic Stimulant Drugs Administered by Inhalation to Patients with Asthma

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Summary: In a double-blind trial of the effect of inhaling three different β -adrenergic stimulants (isoprenaline sulphate 1,000 μ g., orciprenaline sulphate 1,500 μ g., and salbutamol 200 μ g.) and a placebo on ventilatory function in 24 patients with chronic asthma salbutamol was found to have a much longer action than isoprenaline, and it produced a slightly more intense and prolonged effect than orciprenaline. In a double-blind subjective assessment 13 of the 24 patients selected salbutamol as the most effective preparation, while only five preferred isoprenaline and three orciprenaline. Hence salbutamol, given by inhalation, may prove to be the most effective drug at present available for the short-term relief of asthmatic symptoms.

Introduction

The β -adrenergic stimulant isoprenaline is a useful bronchodilator when administered by inhalation, but it has certain disadvantages. These consist of, firstly, a rather short duration of action owing to rapid metabolism by catechol-O-methyl transferase to the inactive 3-methoxy derivative (Paterson *et al.*, 1968), and, secondly, a marked action on cardiovascular β -adrenergic receptors, leading to tachycardia and increased cardiac output (Goodman and Gilman, 1965). Orciprenaline, another specific β -adrenergic stimulant (Engelhardt *et al.*, 1961; Shanks *et al.*, 1967), is effective both by inhalation and by mouth. After inhalation it has a duration of action longer than that of isoprenaline, and is less apt to produce cardiovascular side-effects (Holmes, 1968). In an effort to find a more powerful bronchodilator drug combining prolonged action with a minimum of undesirable β -adrenergic stimulant effects many compounds with structural resemblances to isoprenaline have recently been screened in research laboratories. One of these compounds, salbutamol (AH 3365), has now been released for clinical study, and the purpose of this communication is to assess the bronchodilator activity of this drug compared with that of isoprenaline, orciprenaline, and a placebo, administered by inhalation in each instance. Salbutamol was described by Hartley *et al.* (1968) and by Brittain *et al.* (1968). It differs from isoprenaline in that (a) the meta-OH is replaced by a primary alcohol group—CH₂OH, and (b) the N-isopropyl group is replaced by N-tertiary butyl. The first of these renders the compound stable to catechol-O-methyl transferase, while the second makes inactivation by N-dealkylation unlikely. A compound with these properties should have a prolonged action when inhaled, and should also be effective when given by mouth. Results in animals and preliminary trials in man (Brittain *et al.*, 1968) suggest that salbutamol is indeed a long-acting bronchodilator, effective both by inhalation and by

mouth with little action on the heart. The structural formulae of isoprenaline, orciprenaline, and salbutamol are shown in Fig. 1.

FIG. 1.—Structural formulae of isoprenaline, orciprenaline, and salbutamol.

Plan of Trial

The purpose of the trial was to compare the bronchodilator activity of isoprenaline, orciprenaline, salbutamol, and a placebo consisting simply of inert propellant. It was designed as a 4 × 4 "Latin square," in which the following were administered on consecutive days to each patient: isoprenaline sulphate 1,000 μ g., orciprenaline sulphate 1,500 μ g., salbutamol 200 μ g., and propellant alone.

Each preparation was administered as two "puffs" of a pressurized aerosol, the isoprenaline and orciprenaline being the commercially available products Medihaler-IsoForte and Alupent respectively. (Alupent was repacked at a suitably adjusted concentration in a container to match the others.) The Latin square was repeated six times, the coding of the preparations being changed after each square. In this way all permutations of the four preparations were covered, and since the containers and applicators were identical in appearance it was virtually impossible for bias on the part of either observer or subjects to influence the results.

Forced vital capacity (F.V.C.) and forced expiratory volume in one second (F.E.V.₁) were measured on three occasions at 10-minute intervals before the drugs were administered, except in two instances where by oversight one recording was omitted. The measurements were repeated at 1 minute, 6 minutes, 20 minutes, 50 minutes, 80 minutes, 110 minutes, 140 minutes,

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170 minutes, 230 minutes, and 290 minutes after administration. Three readings were taken on each occasion. In the analysis of results the mean of the highest figures achieved on each of the pretreatment occasions was taken as a "mean best pretreatment figure"; this was the standard with which the best in each group of three post-treatment figures was compared.

A measure of subjective preference was obtained by asking each patient on completion of the trial which treatment had given most relief. Side-effects and other comments were noted if they were mentioned spontaneously. Patients' pulse rates were counted on two or three occasions before treatment and at 1, 6, and 20 minutes after treatment.

The entire procedure was carried out on each occasion by the same technician.

Patient Selection

The patients consisted of 7 men and 17 women, ranging in age from 28 to 71 years (mean 56.3 years). All had severe chronic asthma but had been stabilized for at least six months on treatment with a corticosteroid drug, in most instances prednisolone. They were selected on the basis of having shown a good response to inhaled isoprenaline at previous outpatient attendances, and, in order to ensure that this response would be reproduced in the trial itself, they were accepted for study only if the F.E.V.₁ was between 50 and 75% of the previous highest recording. Those patients who had been receiving prednisolone intermittently were given the drug daily throughout the period of the trial in order to minimize variations in the severity of the asthma. Corticosteroid dosage in terms of prednisolone ranged from 5 to 20 mg. per day.

The mean control value for F.E.V.₁ at the start of the trial was 1,189 ml. (range 390–3,450 ml.), and for F.V.C. was 2,253 ml. (range 880–5,500 ml.).

Results

The increases which occurred in F.E.V.₁ and in F.V.C. after treatment were calculated as percentages of the mean highest pretreatment values, and also in terms of mean total "area under the curve" obtained by integrating the changes in individual values throughout the period of the experiment. The mean highest pretreatment values for isoprenaline, orciprenaline, salbutamol, and placebo were as follows:

Isoprenaline	F.E.V. ₁	1,190	F.V.C.	2,250
Orciprenaline	1,250	2,330		
Salbutamol	1,230	2,300		
Placebo	1,250	2,250

FIG. 2.—Percentage changes in F.E.V.₁ after the inhalation of salbutamol, orciprenaline, isoprenaline, and placebo. FIG. 3.—Percentage changes in F.V.C. after the inhalation of salbutamol, orciprenaline, isoprenaline, and placebo. FIG. 4.—Changes in F.E.V.₁/F.V.C. ($\times 100$) after the inhalation of salbutamol, orciprenaline, isoprenaline, and placebo.

The mean percentage changes in F.E.V.₁ and in F.V.C. are shown graphically in Figs. 2 and 3. The mean changes in F.E.V.₁/F.V.C. ($\times 100$) are shown in Fig. 4. The integrated values for "area under the curve" in respect of F.E.V.₁ and F.V.C. are given in Tables I and II. The patients' preferences at the end of the trial are shown in Table III, and the percentage changes in heart rate from the lowest pretreatment values in Table IV.

TABLE I.—"Area Under the Curve"—Integrated F.E.V.₁ Change

Isoprenaline	64,600	Salbutamol	110,800
Orciprenaline	93,900	Placebo	20,600

A difference of 24,000 or more is significant at the 5% level.

TABLE II.—"Area Under the Curve"—Integrated F.V.C. Change

Isoprenaline	96,300	Salbutamol	160,000
Orciprenaline	126,200	Placebo	46,600

A difference of 40,500 or more is significant at the 5% level.

TABLE III.—Patients' Preferences for Various Treatments

Isoprenaline	5	Placebo	0
Orciprenaline	3	No preference	3
Salbutamol	13		

TABLE IV.—Mean Percentage Change in Heart Rate

Minutes After Administration	Isoprenaline	Orciprenaline	Salbutamol	Placebo
1	13.0*	1.6	3.5	2.9
6	10.8*	-0.6	4.1	2.7
20	3.3	1.1	0.5	0.8

* Significantly different from placebo values ($P < 0.05$).

Placebo

There was a slight and sustained rise in F.V.C. and F.E.V.₁ after the inhalation of placebo, but this change was negligible in comparison with that produced by all three active preparations. The response to placebo was, however, not significantly different from that of isoprenaline at 140, 170, and 190 minutes after inhalation, presumably because by then the pharmacological action of isoprenaline had come to an end.

Isoprenaline 1,000 µg.

The response to isoprenaline was significantly greater at one minute than that observed with either of the other two drugs. The effect reached a maximum at six minutes, was clearly on the wane after less than an hour, and had virtually disappeared at 140 minutes. In terms of F.E.V.₁/F.V.C. ratio patients were at this time no better than after placebo. Isoprenaline produced a significant increase in pulse rate one minute and six minutes after administration.

Orciprenaline 1,500 μ g.

Orciprenaline was longer acting than isoprenaline, its effect on F.E.V.₁ reaching a plateau at between 20 and 120 minutes. The response to this drug was, however, less intense than that observed with either isoprenaline or salbutamol, the maximum mean increase in F.E.V.₁ being 38.7%, as compared with 47.9% for isoprenaline and 47.7% for salbutamol. The effect of orciprenaline on the heart rate did not differ significantly from that of the placebo.

Salbutamol 200 μ g.

Although the response to salbutamol at one minute was not as great as that to isoprenaline 1,000 μ g., there was a subsequent slow increase in effect over the next 60 minutes, in contrast with the rapid decline observed with isoprenaline. In terms of maximum improvement salbutamol equalled isoprenaline on F.E.V.₁ (47.7% *v.* 47.9%) and slightly exceeded it on F.V.C. (35.8% *v.* 30.7%). The bronchodilatation produced by salbutamol was much more prolonged than that produced by isoprenaline, and was well sustained for three hours. Even at five hours after salbutamol the mean F.E.V.₁ was still 26% above the control value, as compared with figures of 8% for isoprenaline, 19% for orciprenaline, and 6% for placebo. The effect of salbutamol on F.E.V.₁ and F.V.C. exceeded that of isoprenaline at 50 minutes and at all subsequent observations.

Compared with orciprenaline, salbutamol produced consistently greater improvement both in F.E.V.₁ and in F.V.C., but the difference was significant ($P < 0.05$) only at 50 minutes in the case of F.E.V.₁ and at 50 and 170 minutes in the case of F.V.C. At most of the other times the value for P lay between 0.1 and 0.05, but support is given to the clinical, if not to the statistical, significance of this difference by the fact that 13 patients selected salbutamol as the best treatment, while only three preferred orciprenaline and five isoprenaline. The effect of salbutamol on heart rate did not differ significantly from that of placebo.

Discussion

The study described in this paper showed that the inhalation of salbutamol in a dose of 200 μ g. provided effective bronchodilatation for a period of at least three hours without producing detectable cardiac stimulation. The bronchodilator activity of this dose of salbutamol was slightly more intense and prolonged than that of 1,500 μ g. of orciprenaline, and equal in peak effect to that of 1,000 μ g. of isoprenaline. Side-effects did not occur with either salbutamol or orciprenaline in the doses specified, but palpitations and tremor have been reported by Holmes (1968) with a higher dose of orciprenaline. Isoprenaline 1,000 μ g. compared unfavourably with both salbutamol and orciprenaline, as the bronchodilator response, though initially more intense, remained effective for less than one hour and was accompanied by tachycardia.

From the data available in this study it is difficult to reach a firm conclusion on the relative therapeutic merits of salbutamol and orciprenaline, because the differences in the effects of these two drugs only rarely achieved statistical significance, and also because the dose of the one or the other may have been sub-optimal. A more conclusive result might have been obtained by observing the bronchodilator response to graduated doses, but this would have been difficult to incorporate into a strictly controlled trial design and probably impracticable, since few patients will tolerate more than four days of this exacting type of investigation. The doses selected for study were those recommended by the manufacturers and normally prescribed in the treatment of asthma. As such, they were considered to provide a fair basis for comparison of the therapeutic value of the two drugs in clinical practice.

Under these circumstances the bronchodilator effect of salbutamol 200 μ g. was slightly superior to that of orciprenaline 1,500 μ g., and in the double-blind subjective assessment it was rated as the best of the four treatments by 13 patients, while only three preferred orciprenaline. These findings suggest that salbutamol, given by inhalation, may prove to be the most effective drug at present available for the short-term relief of asthmatic symptoms.

As a single dose of salbutamol administered by inhalation can provide effective bronchodilatation for three hours, it might be assumed that regular three-hourly inhalation would afford continuous relief of symptoms in chronic asthmatics. Preliminary studies of this kind of therapeutic regimen have, however, shown that the bronchodilator effect of salbutamol, like that of ephedrine when administered regularly by mouth (Laurence, 1966), gradually wanes after a period of one to three weeks. Until more information is available about the frequency with which tolerance can be induced by regular administration, it would be advisable to reserve salbutamol, like other β -stimulants, for the relief of acute asthmatic symptoms, and not to use it in an attempt to maintain continuous bronchodilatation.

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