A double-blind trial of salmefamol, a new bronchodilator

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Summary

Salmefamol is a new sympathomimetic drug with predominantly β_2 actions. In a double-blind trial in a group of twenty-four patients with airway obstruction, we have compared the effect of 100 μ g of salmefamol given by metered aerosol with that of a placebo aerosol. In the same patients we have also compared the aerosols with subcutaneous adrenaline and subcutaneous atropine, the sequence of treatments being determined by a latin square design.

At all times salmefamol had a significantly greater bronchodilator effect than the placebo. Although the effects of atropine and adrenaline were greater at the earlier times of measurement, that of salmefamol was greater at 4 hr.

Introduction

Sympathomimetics are widely prescribed for the treatment of reversible airway obstruction. They can be carried in aerosol form ready for instant use, and they produce their greatest effect within a few minutes of inhalation. Lands *et al.* (1967) distinguished between the cardiac stimulant effect (β_1) and the bronchodilator and vasodilator effects (β_2) of sympathomimetic drugs. This encouraged the search for sympathomimetics whose action on the airway would be greater than on the heart, achieving bronchodilation with minimal cardiac stimulation. A number of drugs producing selective β_2 effect have since been introduced, including salbutamol (Cullum *et al.*, 1969; Kennedy and Simpson, 1969; Choo-Kang, Simpson and Grant, 1969). Salmefamol, AH 3923, is a close chemical relative of salbutamol, AH 3365 (Fig. 1), with similar specificity in laboratory experiments (Hartley *et al.*, 1968). It has been shown in animal experiments to have twice the

bronchodilator effect of salbutamol when they are compared on a weight for weight basis, while the acute oral LD₅₀ in mice and rats is over 1 g/kg (Brittain and Poynter, 1970). This new substance therefore seems likely to be a useful therapeutic agent. Since the work of Crompton (1968) we have investigated the reversibility of airway obstruction by comparing control values of FEV₁ and FVC with those obtained after subcutaneous injection of adrenaline on the first day and subcutaneous injection of atropine on the next. The patients in this study had all been referred from the wards of the University Department of Respiratory Diseases for such an assessment. We therefore compared the effects of an aerosol of salmefamol and a placebo, in a double-blind manner, with the two standard bronchodilators employing a within-patient study.

Subjects

Twenty-four patients participated in the trial. Their age, sex and other relevant details are shown in Table 1. All of them were studied while in-patients of the University Department of Respiratory Diseases. Every patient had previous spirometric evidence of airway obstruction, as shown by a reduction in the ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC). The trial was conducted over a period of 5 days, during which no routine bronchodilator therapy was given. Nine of the patients had been taking prednisolone before admission to hospital; they remained on their usual dose during the period of the trial. The twenty-four patients all agreed to take part after the nature and aim of the study had been explained to them.

The pre-treatment FEV₁ and FVC of the patients covered a wide range, for example, the values for patient 22 were close to her predicted levels, while those of patient 16 were very low. Analysis of covariance was used to allow for these differences in the pre-treatment values by adjusting the increases

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FIG. 1. Structural formulae of (a) salbutamol and (b) salmefamol.

TABLE 1. Details of patients studied

Patient	Sex	Age	First pre-treatment		Predicted*		Whether on corticosteroids
			FEV ₁ (ml BTPS)	FVC (ml BTPS)	FEV ₁ (ml BTPS)	FVC (ml BTPS)	
1	M	65	800	1925	2300	3200	No
2	M	55	870	2600	2780	3800	No
3	F	51	1370	2150	2300	2700	Yes
4	F	34	1900	3750	2800	3300	No
5	F	15	1900	2650	2750	3050	No
6	F	20	1750	2800	2820	3350	No
7	F	62	590	1720	2050	2500	Yes
8	M	73	1230	2710	2100	3150	Yes
9	F	77	920	1330	1300	1500	No
10	F	71	500	1400	1900	2350	No
11	M	68	900	1950	2950	4250	No
12	M	58	1520	3200	2650	3550	No
13	M	62	1890	3930	2800	2970	Yes
14	M	18	2250	3050	3810	4400	No
15	M	17	2350	4400	3450	3800	Yes
16	M	60	470	2720	2520	3600	No
17	F	75	1120	1460	1500	1800	Yes
18	M	67	580	1840	2220	3100	Yes
19	F	53	760	1640	2000	2400	Yes
20	M	54	2350	4000	3000	4000	No
21	M	73	1000	2000	2400	3700	No
22	F	18	3100	4200	3300	3800	Yes
23	M	41	1800	3525	3200	4000	No
24	M	63	900	1500	2600	3550	No

* Predicted values from Cotes (1968).

in FEV₁ and FVC following treatment (Armitage, 1971a).

Procedure

FEV₁ and FVC were measured using an electronically timed spirometer (McKerrow, McDermott and Gilson, 1960). All measurements were made by experienced laboratory technicians or by one of us (D.B.). The same person made all the measurements on a given patient in all but two instances. The highest value of three technically satisfactory attempts for each variable was used for the statistical analysis (Freedman and Prowse, 1966).

The treatments consisted of (1) placebo aerosol (propellants only); (2) salmefamol aerosol (50 µg per

metered dose) [(1) and (2) by inhalation]; (3) adrenaline 0.5 mg; (4) atropine 0.6 mg [(3) and (4) by subcutaneous injection].

Salmefamol and the placebo were administered from identical aerosol canisters, each marked with a number code whose key was unknown to the investigators. The canister was shaken and discharged once into the air. One puff of aerosol was then administered by a technician whilst the patient slowly inhaled from functional residual capacity. The patient continued breathing in until total lung capacity was reached and then, after a short pause, exhaled normally. A second puff was administered in the same way about one minute later. This gave a total dose of 100 µg of salmefamol. The atropine

and the adrenaline were given by subcutaneous injection. The adrenaline injection was given slowly, taking up to 2 min. It was therefore not possible to use a double-blind procedure for these drugs. Each treatment was administered by 10 a.m. on consecutive mornings and was preceded by the initial measurements of the FEV₁ and FVC. The measurements were repeated 20, 80, 120 and 240 min after the treatment. On the fifth day no treatment was given but a final measurement of FEV₁ and FVC was made at 10 a.m.

All patients received each of the four treatments during the first 4 days of the trial. The order of treatments was determined by a latin square design suggested by Professor D. J. Finney. Each subgroup of four patients formed a 4 × 4 latin square and so all twenty-four of the possible sequences of the four treatments were used. With such a design, each patient acts as his own control, thus improving the precision with which effects of treatment are estimated. Any effect of the sequence of treatments can also be calculated and allowance made for this in the statistical analysis of comparisons (Armitage, 1971b).

Results

The results below are presented in terms of the grouped values. Results of individual measurements on all patients can be obtained from the authors. The value of such detailed information has been stressed by Oldham and Hughes (1972).

The changes in FEV₁ resulting from the different treatments, including the placebo, at the four different times after the dose are shown in Table 2. The values are expressed as the mean increases in FEV₁ over the pre-treatment values. The time course of the responses to the drugs is shown in Fig. 2. Salmefamol can be seen to produce an effect significantly greater than that of the placebo at all times up to 240 min, the total duration of observation ($P < 0.05$).

TABLE 2. Mean increases in FEV₁ (ml BTPS) over pre-treatment values

Drug	Time after treatment (min)			
	20	80	120	240
Placebo aerosol	33	51	77	6
Salmefamol aerosol	216	228	222	215
Adrenaline s.c.	281	292	318	128
Atropine s.c.	311	372	347	97
Standard error of the difference between two drug means	51.2	53.4	60.0	56.0

The difference between two drug means is significant at (approximately) the 5% level when the observed difference between the means is greater than twice the standard error of the difference.

FIG. 2. Mean changes in FEV₁ (ml BTPS) resulting from the different treatments: atropine (●—●), salmefamol (△---△), adrenaline (■—■) and placebo (○---○). All treatments were given at zero time.

Atropine and adrenaline, in the doses used, caused greater responses than salmefamol at 20, 80 and 120 min. At 240 min, however, the response to salmefamol had persisted and the mean value for the increase in FEV₁ was greater than that following atropine by more than twice the standard error of the difference of the means at this time (Table 2). This difference is statistically significant at the 5% level. The difference between salmefamol and adrenaline at 240 min is not statistically significant.

The pre-treatment values of FEV₁ on the first day of the trial (Table 1) cover a wide range. Because of this it was thought possible that a different picture might emerge if changes in FEV₁ were expressed as a percentage of the pre-treatment values rather than in absolute terms. However, analysis of these percentages revealed little alteration in the patterns of response.

The mean increase in FVC resulting from the different treatments is given in Table 3. At all times salmefamol showed a larger increase than occurred with the placebo. Adrenaline and atropine gave higher values up to 120 min but the effect of these drugs on FVC had declined by 240 min. Although the effect of salmefamol on FVC at 240 min was greater than that of the other active drugs, the differences did not reach statistical significance. Table 3 shows

TABLE 3. Mean increases in FVC (ml BTPS) over pre-treatment values

Drug	Time after treatment (min)			
	20	80	120	240
Placebo aerosol	52	134	150	63
Salmefamol aerosol	130	203	231	200
Adrenaline s.c.	269	368	300	179
Atropine s.c.	290	365	353	117
Standard error of the difference between two drug means	62.5	67.2	62.6	63.2

The difference between two drug means is significant at (approximately) the 5% level when the observed difference between the means is greater than twice the standard error of the difference.

the placebo to have had a pronounced effect on FVC at 80 and 120 min.

The analysis of the latin square showed that treatment sequence did not affect the average response of FEV₁ or FVC. No carry over of the effect of any drug to the next day was detected.

No side effects were reported, or noticed after inhalation of either aerosol.

Discussion and conclusions

This study has demonstrated clearly that salmefamol produces bronchodilatation in man. Examination of the FEV₁ curve (Fig. 2) reveals a consistent and prolonged effect after salmefamol lasting until the end of the study (4 hr). The statistical analysis has produced no evidence that salmefamol affected the next day's pre-treatment FEV₁. These facts would suggest that it is effective for between 4 and 24 hr. The nature of this trial did not allow precise determination of the end-point. The clinical value of this new bronchodilator may lie in its long action, a property similar to that of salbutamol; it will therefore be important to compare its potency and duration of action directly with those of salbutamol over a longer time period. It will be of practical value to assess the effect of different doses of this new drug. In addition, it will be important to

monitor the effects upon heart rate and blood pressure to see whether the specificity for β_2 adrenergic receptors shown in animals is also applicable in man.

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