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COMPARISON OF SALMEFAMOL AND SALBUTAMOL IN PATIENTS WITH CHRONIC AIRWAYS OBSTRUCTION

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1 Inhaled salmefamol, in doses of 100 μg and 200 μg has been compared with inhaled salbutamol, in a dose of 200 μg, and with placebo in patients with airways obstruction.

2 Both salmefamol and salbutamol are potent bronchodilators with a significantly superior action over placebo at all times up to 8 h after treatment.

3 The mean peak percentage increases in FEV_1 produced by the three active preparations were similar. The decline from peak values was significantly slower with salmefamol than with salbutamol. Neither drug produced tachycardia.

Introduction

Previous studies (Kennedy & Dash, 1972; Bainbridge, McHardy, Hoare & Dash, 1975) in patients with airways obstruction have shown that salmefamol, a new sympathomimetic drug with predominantly β_2 actions, is an effective drug which acts for at least 4 h, and has a peak effect after approximately 1 hour. In the present study we aimed to compare salmefamol in two different doses with the commonly used bronchodilator, salbutamol, and with placebo, studying not only peak effects but also the duration of the responses. Both bronchodilator and cardiac effects were observed.

Method

Patients

The twenty-four patients in the study were in-patients admitted by their physician for assessment of airways obstruction and were aged between 16 and 60 years. None of the patients had hypertension or overt cardiac disease. Informed consent was always obtained from the patient and the study was approved by the ethical committee of the Hospital.

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Patients taking sodium cromoglycate or corticosteroids were not admitted to the study.

Design of study

The study was designed as a double-blind, placebo controlled, within patient comparison of the drugs, the order of treatments being randomised in six 4 x 4 latin squares. Each of the patients received the treatments in a different order so that all possible sequences of administration of the four inhalers were employed.

Drugs and dosages

The treatments were as follows:

(1) Salmefamol (100 μg) given as two 50 μg puffs
(2) Salmefamol (200 μg) given as two 100 μg puffs
(3) Salbutamol (200 μg) given as two 100 μg puffs
(4) Placebo given as two puffs.

The drugs and placebo were given from identical aerosol canisters. Neither the patient nor the observer was aware of which preparation was being used on any day.

Table 1 Details of patients and peak responses of FEV_1 and FVC (litres BTPS)

Patient	Sex	Age (years)	Predicted normal		Pre-treatment values (means of days 1-4)		Peak values after each treatment							
							Placebo		Salmefamol (100 μg)		Salmefamol (200 μg)		Salbutamol (200 μg)	
			FEV_1	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC	FEV_1	FVC
1	M	25	4.00	4.70	2.02	3.37	1.94	3.40	2.46	3.85	2.60	3.85	2.65	4.15
2	M	53	2.63	3.50	0.82	1.96	0.85	2.00	1.10	2.60	1.15	2.39	1.20	2.53
3	F	16	2.90	3.20	1.47	2.03	1.68	2.10	1.95	2.70	1.68	2.29	1.83	2.30
4	M	37	3.60	4.40	0.81	3.31	1.05	4.22	1.22	4.61	1.25	4.55	1.07	4.15
5	F	47	2.62	2.86	3.17	3.88	3.35	4.10	3.40	4.10	3.40	4.00	3.33	3.97
6	F	44	2.43	2.50	1.96	2.66	2.10	3.00	2.03	2.79	2.07	2.71	2.00	2.85
7	F	50	2.70	3.00	1.67	2.61	2.33	3.44	2.15	3.25	2.16	3.20	2.72	3.54
8	M	42	3.16	3.96	1.66	3.39	1.68	3.23	2.17	4.10	2.33	4.40	2.30	4.00
9	F	55	2.35	2.55	0.72	2.21	0.80	2.17	0.75	2.35	0.91	2.50	0.86	2.35
10	M	37	3.67	4.60	1.67	4.40	1.73	4.48	1.96	5.09	2.05	4.79	2.05	5.13
11	M	50	3.20	4.20	1.07	2.83	1.23	3.20	1.02	3.05	1.27	3.75	1.38	3.51
12	F	57	2.35	2.50	0.95	2.06	1.07	2.12	0.94	2.00	1.03	2.17	1.08	2.30
13	F	59	2.15	2.25	0.90	1.65	0.92	1.65	1.11	1.90	1.14	2.00	1.25	2.17
14	M	56	2.92	3.95	0.80	1.89	0.77	1.97	0.94	2.51	0.96	2.10	0.85	2.00
15	M	27	3.70	4.34	2.92	4.09	3.05	4.35	3.26	4.35	3.27	4.29	3.36	4.45
16	M	60	2.67	3.65	1.19	2.54	1.21	2.65	1.45	3.30	1.47	3.30	1.49	3.12
17	M	49	2.90	3.80	0.90	2.56	0.85	2.61	1.21	3.30	1.21	3.36	1.22	3.17
18	F	26	2.98	3.08	2.15	2.95	2.16	3.15	2.30	3.20	2.25	3.10	2.25	3.10
19	F	57	2.34	2.52	1.12	2.27	1.18	2.35	1.14	2.23	1.35	2.52	1.56	2.75
20	M	36	3.72	4.61	2.98	3.81	3.53	4.30	3.55	4.35	3.52	4.42	3.48	4.30
21	F	41	2.80	3.08	1.73	2.93	2.20	3.40	2.45	3.70	2.40	3.84	2.44	3.75
22	M	58	2.89	3.96	0.71	2.03	0.76	2.22	0.88	2.47	0.96	2.63	0.89	2.40
23	M	17	4.02	4.70	3.27	5.03	4.17	5.69	4.71	5.85	3.28	4.92	4.96	5.91
24	M	43	3.69	4.62	1.55	4.47	1.90	3.87	2.00	5.31	1.65	4.82	1.75	4.89

Experimental procedure

The forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC) were measured using an electronically timed spirometer (McKerrow, McDermott & Gilson, 1960), volumes being recorded at body temperature and pressure saturated with water vapour (BTPS). All measurements were made by experienced laboratory technicians or by one of us (I.A.C.). The highest value obtained from three technically satisfactory attempts was used for statistical analysis. Electrocardiographic recordings were made on a Sharp MT 23 machine, a 30 s lead II strip being taken before the forced expiratory manoeuvres. The bronchodilator effects and the effects of the drugs on heart rate were compared using analysis of variance.

No bronchodilator preparation was given for 12 h prior to the first reading at 09.00 h on the first day. After arrival at the laboratory the patient rested for 10 minutes. With the patients in a sitting position a 30 s ECG recording was then made and FEV_1 and FVC were measured. Two puffs of the inhaler designated for that day were given, each puff being taken during inspiration from residual volume. The ECG, FEV_1 and FVC recordings were repeated at 1, 2, 4, 6 and 8 h thereafter. On the following 3 days the procedure was repeated using a different inhaler each day, the sequence for each patient having been determined by the latin square design. Finally, at 09.00 h on the fifth day the ECG and spirometric measurements were recorded.

Results

Twenty-four patients, fourteen men and ten women, were studied and are described in Table 1 in terms of sex, age, ventilatory capacity and peak responses to each drug. The mean pre-treatment values of FEV_1, FVC and the ratio of FEV_1/FVC on the days each of the four inhalers were used were similar from day to day (Table 2). These pre-treatment mean values of FEV_1 were less than 60% of the mean predicted normal value for the group, which was 2.93 litres, s.e. mean 0.186.

Figure 1 shows the mean changes in FEV_1, expressed as percentages of the pre-treatment value, at 1, 2, 4, 6 and 8 h after each preparation. Analysis showed that both doses of salmefamol were significantly superior to placebo at all times, as was salbutamol ($P < 0.01$). It can also be seen that at all times salmefamol (100 μg) had a greater effect than salbutamol (200 μg) and that salmefamol (200 μg) gave an even greater response. In the group as a whole, at 6 and 8 h after

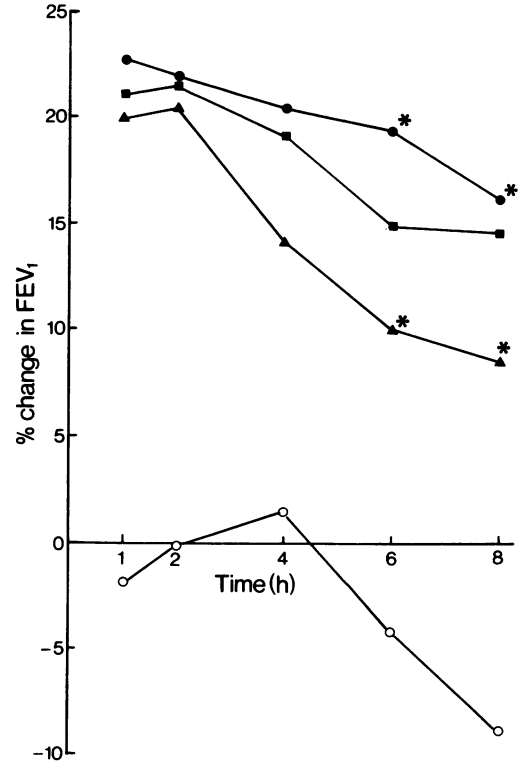

Figure 1 Mean ($n = 24$) percentage change in FEV_1 v. time after inhalation of salmefamol (200 μg ●), salmefamol (100 μg ■), salbutamol (200 μg ▲) and placebo (○). * indicates differences between the active preparations which are significant at the 5% level. All other differences between the active preparations are not statistically significant.

Table 2 (Mean ($n = 24$) pre-treatment FEV_1, FVC and FEV_1/FVC% on each treatment day

Inhaler	*FEV_1 (litres BTPS)*	*FVC (litres BTPS)*	*FEV_1/FVC%*
Placebo	1.66	3.00	55%
Salmefamol (100 μg)	1.57	2.93	54%
Salmefamol (200 μg)	1.51	2.86	53%
Salbutamol (200 μg)	1.62	3.03	54%
s.e. of each mean*	0.051	0.059	

* Calculated from the residual mean square of the analysis of variance table

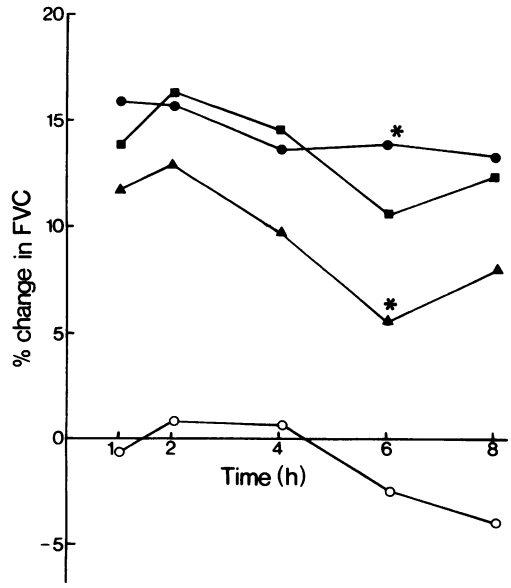

Figure 2 Mean (n = 24) percentage change in FVC v. time after inhalation of salmefamol (200 μg ●), salmefamol (100 μg ■), salbutamol (200 μg ▲) and placebo (○). * indicates differences between the active preparations which are significant at the 5% level. All other differences between the active preparations are not statistically significant.

treatment salmefamol (200 μg) was significantly superior to salbutamol ($P < 0.05$). The changes in FVC are displayed in the same fashion in Figure 2. At all times both doses of salmefamol produced a greater effect than did salbutamol (200 μg). A statistically significant difference between salmefamol (200 μg) and salbutamol (200 μg) was evident at 6 h after drug administration ($P < 0.05$). The three drugs were at all times significantly superior to placebo ($P < 0.01$).

Analysis of carry-over effect, using the orthogonal latin squares, showed no statistically significant differences between the treatments although there was a tendency for patients to show a better response to treatment on the day after they had received placebo. On the day following the placebo treatment the baseline FEV_1 was lower than it was on the days after the other three treatments but the differences do not reach the 5% level of significance.

The mean heart rates before and at each time after treatment are shown in Table 3. Neither the placebo nor any of the active treatments increased the heart rate. In fact, the mean rates after all treatments were lower than the mean pre-treatment values. Again, analysis of carry-over effect revealed no significant differences between treatments. No side effects were noticed by the patients.

Discussion

The use of the latin square design in a bronchodilator comparison such as this has two advantages over simple randomisation. First, by using a different order of treatment for each patient the effects of any systematic variation in ventilatory capacity, for example a tendency to improve during the first days in hospital, are prevented from biasing the comparison of the treatments. Simple randomisation might not protect the comparison in such a manner and more patients would be needed to achieve the same level of precision. Secondly, with four treatments to compare, using the latin square design in a population of twenty-four patients will not only allow all possible orders of treatment to be given but also allows each treatment to follow any other treatment exactly the same number of times. Thus carry-over effects from day to day can easily be investigated.

Table 3 Mean (n = 24) heart rate before and at various time intervals after inhalation of salmefamol, salbutamol or placebo

		Heart rate (beats/min)				
		Time after treatment (h)				
Inhaler	*Pre-treatment*	*1*	*2*	*4*	*6*	*8*
Placebo	80.4	75.3	75.3	78.3	76.3	76.1
Salmefamol (100 μg)	82.2	78.7	75.2	79.5	75.5	72.3
Salmefamol (200 μg)	83.6	79.3	78.5	75.3	76.9	71.8
Salbutamol (200 μg)	81.7	78.3	78.0	76.2	75.7	72.3
s.e. of each mean*	1.3	1.2	1.3	1.1	1.2	1.3

* Calculated from the residual mean square of the analysis of variance table

The three active preparations showed similar peaks in the mean percentage increases of FEV_1 at 1 h and 2 h, and 8 h after administration, were still producing statistically significant bronchodilation relative to placebo. The greatest individual improvement in FEV_1 8 h after receiving salmefamol (200 μg) was 0.7 litres, the pre-treatment value having been 1.6 litres. The dose-dependent effect observed by Kennedy & Dash (1972) at times up to 4 h when comparing the effects of the two doses of salmefamol on the indirect maximum breathing capacity was less apparent in our study, but at later times a dose-related effect on FEV_1 was noticeable. Lal, Dash & Gribben (1974), analysing peak flow recorded at home by patients themselves, noted that salmefamol had a more prolonged bronchodilator effect than salbutamol. The present work confirms the superiority of salmefamol over salbutamol using spirometric tests performed in the laboratory. This longer action of salmefamol is possibly due to the fact that one of its pre-conjugation metabolites, AH4553, possesses bronchodilator properties (Hartley, Jack, Lunts & Ritchie, 1968; Evans, Shenfield & Paterson, 1974).

The changes in ventilatory capacity on the days that placebo was given probaly represent diurnal variation. The slightly better response to treatment noted on the day after placebo was given might be a consequence of the fact that on the day following placebo the baseline FEV_1 was lower than on the days following the three active inhalers. The differences between these pre-treatment FEV_1 values do not, however, reach the 5% level of significance.

In the doses used none of the drugs produced cardiac side effects in terms of increased heart rate or the appearance of extrasystoles. This indicates that both compounds exhibit a high degree of β_2-adrenoceptor selectivity in man, a selectivity also demonstrated in the guinea-pig (Evans, Shenfield & Paterson, 1974).

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