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NEW BRONCHODILATOR AEROSOL, SALMEFAMOL, IN ASTHMA

By

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Sympathomimetic bronchodilator drugs may be administered by injection, by mouth or by inhalation. Injection therapy is usually reserved for acute asthma when the patient is unable to inhale effectively and a quick response is required. With the advent of metered aerosols, inhalation therapy is superseding the oral route, since, when these drugs are given by inhalation, the effect is better than after oral administration, although the dose used is much smaller. Moreover, the incidence of side effects is lower after inhalation. It is our general policy to give sympathomimetic bronchodilators by metered aerosols.

Comparative trials of the various newer adrenergic agents have shown orciprenaline and salbutamol to act for longer and to have less action on the heart than isoprenaline. Salmefamol (AH3923) is a new addition to this class of compound. It has the formula paramethoxyphenyl-1-isopropylamino-1 (4-hydroxy-3-hydroxymethyl) phenyl ethanol. It is chemically related to salbutamol, and has the same specific action on bronchial muscle in animals (1). In asthmatics, single doses of this drug by metered aerosol have been shown to have a longer duration of action than orciprenaline and salbutamol (2, 3, 4).

The aims of the trial reported here were twofold. First, we wished to assess the effect in chronic asthma of aerosol salmefamol given 6 hourly for 3 months. Second, we wished to

TAl
Summary of Patients' Details, including usual

Patient characteristics						
Patient	Sex	Age (yrs)	Occupation	Duration of asthma (yrs)	Airway obstruction (grade§)	Associa- tion emphysema
C.L.	M	60	School-teacher	60	4/Severe	++
A.F.	F	34	Housewife	11	3/Moderate	
A.S.	F	58	Housewife (Ex-pottery worker)	15	4/Severe	
A.R.	M	17	Lens grinder (trainee)	10	4/Severe	+
D.E.	F	29	Housewife	18	3/Severe	
N.H.	F	57	Cleaner (part-time)	55	3/Moderate	++
H.F.	M	53	Farmer (retired)	27	4/Severe	+++
W.S.	M	39	Manager— hardware shop	39	4/Mod.Sev.	+
F.S.	M	69	Kiln fireman (retired)	20	4	++
C.B.	M	74	Metallurgist (retired)	28	4/Severe	+
M.E.	F	63	Housewife	8	4/Moderate	
A.B.	M	55	Sales merchant	10	4/Moderate	+
S.W.	F	28	Lithographer (part-time)	25	2/Severe	+
C.J.	M	49	Joiner	14	4/Severe	++
J.K.	M	71	Builder	12	4/Moderate	+
W.S.	M	59	Ex-miner (now Remploy)	17	4/Mod.Sev.	++
J.S.	F	50	Housewife	30	4/Severe	+

Therapy and the Effect of Salmefamol Aerosol.

Atopic	Blood eosinophilia	Aetiology of asthma	Therapy				Salmefamol effect	
			Intal	Becotide	Steroids	Usual inhaler*	Patient's preference*	Objective improvement
+	?	Pollens, House mite, Moulds	+	+	+	V	S	+
+	?	?	+	+	+	A	S	+
		?	+	+	+	V	V	
+	+	House mite	+	+		V	S	+
	+	?	+	+	+	V	S	+
+	+	?	+	+	+	V	S	+
	?	Bird-fanciers lung	+	+	+	A	S	+
+	±	House mite, Grass pollen	+	+		V	V	+
		? Industrial emphysema	+			V	S	+
		?	+	+		V	S	
?		?	+	+	+	A	S	
+		Grass pollen, House mite	+			V	S	+
+	+	Grass pollen, House mite	+	+		A	S	+
		?	+	+	+	A	S	+
	+	?	+	+	+	V	V	+
		Scalded bronchial tree	+		+	V	S	+
+	?	Grass and tree pollens, etc.	+	+	+	V	V	+

Patient	Sex	Age (yrs)	Patient characteristics				A
			Occupation	Duration of asthma (yrs)	Airway obstruction (grade§)	Associated emphysema	
J.H.	F	58	Housewife	19	4/Severe	+	
E.W.	M	48	Ex-sanitary caster	19	4/Severe	+	
A.C.	F	52	Housewife	12	4/Mod.Sev.	±	
A.A.	M	67	Foreman cyanide plant (retired)	12	3/Mod.Sev.	++	
P.R.	M	22	School-teacher	22	3/Severe	++	
V.M.	M	58	Ex-joiner	11	4/Moderate	++	
H.B.	F	32	School canteen asst.	3	4/Moderate	+	
P.G.	F	34	Housewife	31	2/Moderate	+	

* A = orciprenaline (Alupent); I = isoprenaline (Medihaler Iso-forte); V = salbutamol (Ventolin); S = Salmefamol.

know whether the effect of the drug was likely to diminish with continued regular use during 3 months.

PATIENTS AND METHODS

Twenty-five asthmatic adult out-patients (fourteen men and eleven women), receiving maintenance bronchodilator aerosols (2 metered doses q.d.s.), were investigated. All patients had attended regularly for a number of years. At each attendance (which was at roughly the same time of day) their indirect maximum breathing capacity (IMBC) was derived from the mean of four forced expiratory spiograms; this was done both before, and 5 minutes after, 1 min of inhalation of 1:1000 adrenaline hydrochloride from a Collison inhaler. All patients recorded their symptoms during the day and during the night on a diary card. Symptoms were graded according to a simple scoring system: the

(continued)

Atopic	Blood eosinophilia	Aetiology of asthma	Therapy				Salmefamol effect	
			Intal	Becotide	Steroids	Usual inhaler*	Patient's preference*	Objective improvement
	+	?	+	+	+	V	S	
	+	?	+		+	A	S	+
	?	?	+	+	+	V	S	+
	?	? Isocyanate	+		+	I	I	N.R.
+	+	Grass pollen, House mite	+	+		V	V	
	?	?	+	+		V	S	+
+	+	? Allergic aspergillosis and House mite				V	S	
+		Grass pollen, House mite				V	V	

§ Kennedy (1972).

N.R. = IMBC not recorded.

higher the score, the better the control of asthma. Data available for the 3 months before starting salmefamol were scrutinised—eighteen patients had used salbutamol, 6 orciprenaline and 1 isoprenaline aerosol during this time. All patients were receiving sodium cromoglycate and eighteen were steroid-dependent. Clinical details are summarised in Table 1.

Salmefamol was substituted for their usual aerosol and given for 3 months at the same dosage, 2 inhalations (equivalent to 200 µg) q.d.s. During this time, the patients continued recording their symptoms and reporting for spirometry as before; and they were asked how the new aerosol compared with their previous treatment and whether they developed any adverse reactions.

After 3 months of salmefamol therapy, most patients reverted to their usual bronchodilator and were investigated as before. The asthmatic state and symptoms of the patients were then analysed during these three periods (i.e. pre-salmefamol, salmefamol and post-salmefamol periods) and the results compared.

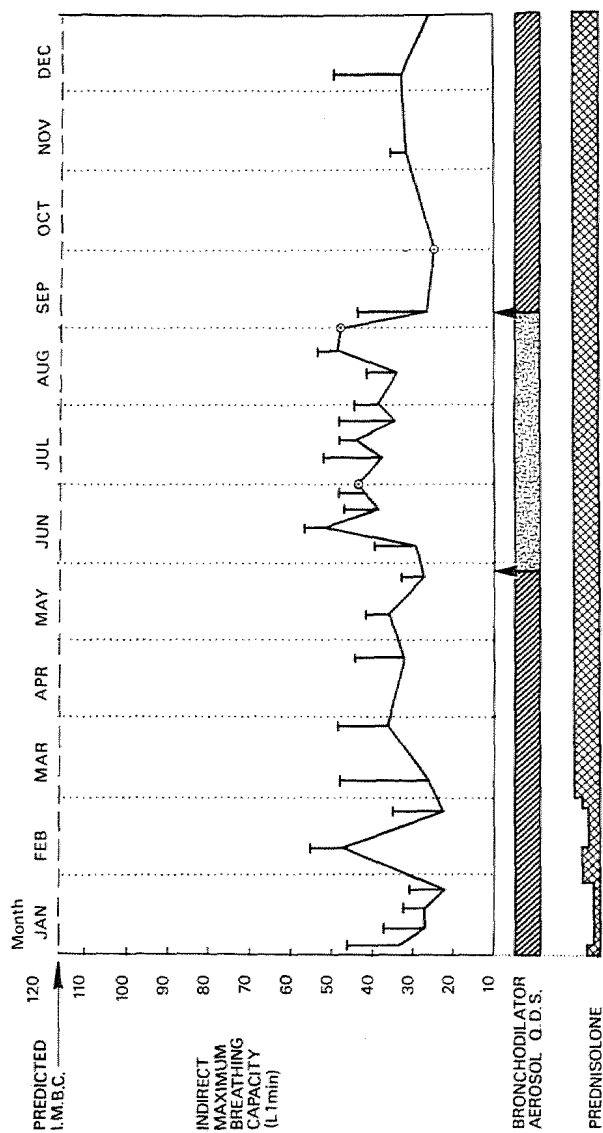


Fig. 1. Case 1 (W.S.) Annual asthma chart for 1972.

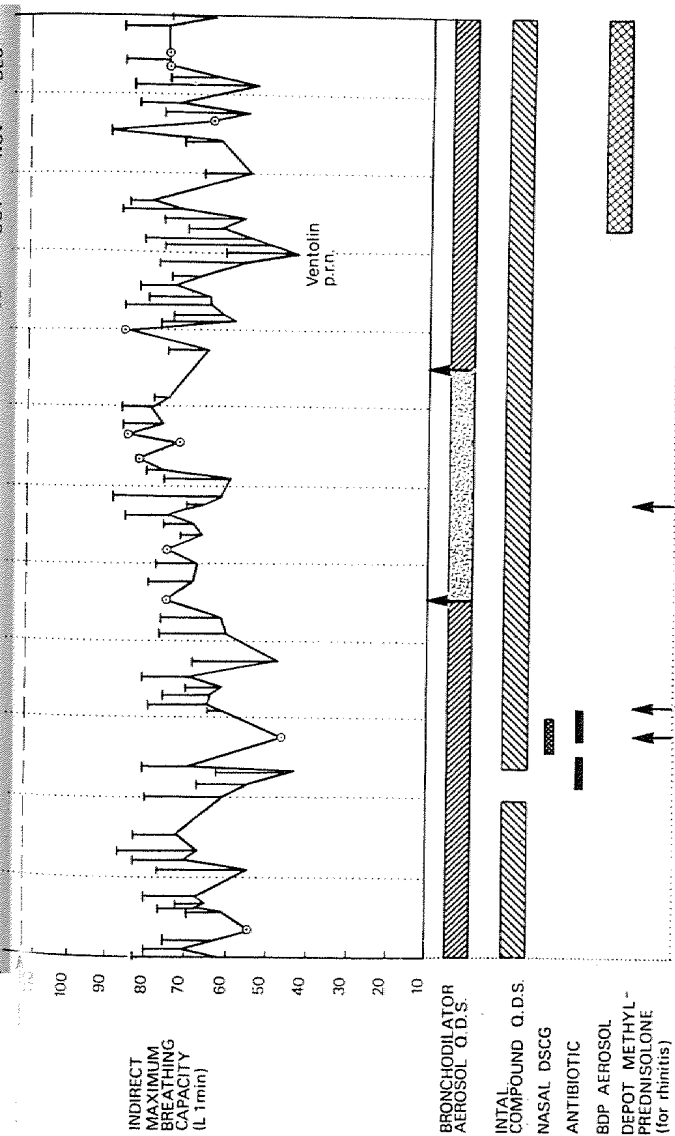


Fig. 2. Case 2 (A.B.) Annual asthma chart for 1972.

After adrenaline; ○ pre- and post adrenaline values identical

Before adrenaline

salbutamol aerosol

salmetamol aerosol

RESULTS

Twenty-four patients used the new aerosol regularly for at least 3 months; one patient withdrew from the trial after 3 weeks.

Illustrative Cases

The annual asthma charts of two patients are shown in Figs. 1 and 2 as examples of the data available for analysis.

Case 1 (W.S.) is a man aged 59 years. In 1955, when he was working as a coalminer, there was an underground explosion and fire and he incurred severe burns to the face, hands and throat; he probably also incurred blast injury to the lungs. He has had asthma and increasing exertional dyspnoea since. Lung volume studies indicate the progressive development of emphysema over the years. There has been a progressive increase in the residual volume, and a progressive deterioration in the I.M.B.C. Throughout the years, he has always shown a substantial response to aerosol adrenaline. He has been on ACTH or steroids for many years.

The 1972 asthma chart (Fig. 1) shows a marked improvement in the pre-adrenaline IMBC values and a reduced response to aerosol adrenaline whilst on salmefamol, compared with the periods when he was on salbutamol. There is little change in the post-adrenaline IMBC values when on either drug.

Case 2 (A.B.) a 57-year-old male has had severe summer asthma during May and June since 1962, with increasing asthmatic episodes over the autumn and winter months. Sputum at times has been loaded with eosinophils, but blood eosinophilia has not been detected. He has marked (+++) skin reactions to grass pollen, house dust and house mites; but no other obvious clinical or skin hypersensitivity and no family history of asthma. Since he first attended in 1967, he has been having sodium cromoglycate four times daily with considerable benefit. In the past he has had occasional corticosteroid therapy at the height of the grass pollen season. Over the years he has shown a remarkably consistent response to aerosol adrenaline (IMBC usually about 60 L/min increasing to 80 L/min after adrenaline).

In 1972 (Fig. 2), he was on salbutamol and sodium cromoglycate plus isoprenaline (Intal Compound) q.d.s. up to mid-May when salmefamol was substituted for the salbutamol (Ventolin). Throughout the 3 months on salmefamol (apart from three occasions at the end of June when high pollen counts were recorded locally), the pre-adrenaline IMBC was in the region of 80 L/min, and there was little further bronchodilatation after aerosol adrenaline. At the height of the grass pollen season on June 30th, hay-fever symptoms were very severe, but cleared within 24 h after a single intramuscular injection of depot methylprednisolone (Depo-Medrone).

After the 3 months on salmefamol he reverted to salbutamol and the pre-adrenaline IMBC values dropped to values present before the salmefamol

period—i.e. pre-adrenaline value usually in the region of 60 L/min and increasing to the region of 80 L/min after aerosol adrenaline. Later in the year, beclomethasone dipropionate aerosol was given, together with salbutamol and sodium cromoglycate.

This is an example of consistent improvement in pre-adrenaline IMBC values when on salmefamol 200 μg q.d.s., compared with salbutamol 200 μg q.d.s. The post-adrenaline values remain unchanged.

IMBC and Reversibility with Adrenaline Solution

One patient did not attend for measurement of IMBC, but he recorded symptom scores throughout. The mean IMBCs before and after adrenaline during the 3 months of salmefamol treatment were compared with the previous and subsequent 3-month periods when on their usual bronchodilator aerosol. A paired t-test was used for comparison. There was a highly significant improvement ($P < 0.005$) in the pre-adrenaline values after changing to salmefamol, but there was no significant difference in the post-adrenaline values. After return to the usual aerosol, there was a deterioration in the pre-adrenaline values which was statistically significant at the 1 per cent level; but there were no significant differences in the post-adrenaline values. There were no differences in either the pre- or post-adrenaline values between the first and last periods of therapy with usual aerosol (Table 2 A).

The mean IMBC before adrenaline during the salmefamol period was higher than that during the preceding period on the 'usual' aerosol in 18 patients and lower in 6 patients ($\chi^2 = 5.04$, l.d.f.; $P < 0.05$). If plotted sequentially in the order in which therapy started, the 5 per cent significance boundary is reached in favour of salmefamol after 17 preferences (Fig. 3, curve A).

When the salmefamol period was compared with the succeeding 'usual' aerosol period the mean IMBC before adrenaline on salmefamol was higher in 17 patients and lower in 5 patients. This difference was statistically significant using the chi-squared test ($P < 0.02$), but not when plotted on a sequential analysis chart in the order in which treatments com-

TABLE 2

Mean Indirect Maximum Breathing Capacities (IMBC) Before and After Inhalation for 1 min of 1:1000 Solution of Adrenaline Hydrochloride of (A) Each Treatment Period, (B) Each Half of the Salmefamol Treatment Period. Also Indicated are the Results of Paired 't'-tests when Statistically Significant (the Absence of any Indication Denotes $P > 0.05$).

Trial period	Mean IMBC (L/min)	
	Pre-adrenaline	Post-adrenaline
A.		
Usual aerosol before salmefamol	47.8*	57.4
Salmefamol	53.8* §	58.9
Usual aerosol after salmefamol	47.9§	57.1
B.		
1st half salmefamol period	53.3†	54.3†
2nd half salmefamol period	59.5†	58.6†

§ $P < 0.02$

* $P < 0.005$

† $P < 0.001$

menced (Fig. 3, curve B). There were no statistically significant differences in the post-adrenaline values.

Fifteen patients had a higher mean pre-adrenaline IMBC while on salmefamol than in both the preceding and succeeding periods on their 'usual' aerosol. Two patients had lower mean IMBC when on salmefamol than in either of the other two periods. During the salmefamol period, four patients had a mean IMBC intermediate between the two 'usual' aerosol periods. The chi-squared test shows that these differences were statistically significant in favour of salmefamol ($P < 0.01$). Three patients did not have a succeeding period of 'usual' aerosol because they wished to continue with salmefamol.

The possibility of a diminished bronchodilator effect as a result of prolonged regular treatment was studied by dividing the 3-month salmefamol period in half. The mean IMBCs during the two halves were compared by a paired t-test. Both the pre- and post-adrenaline values in the second half of the

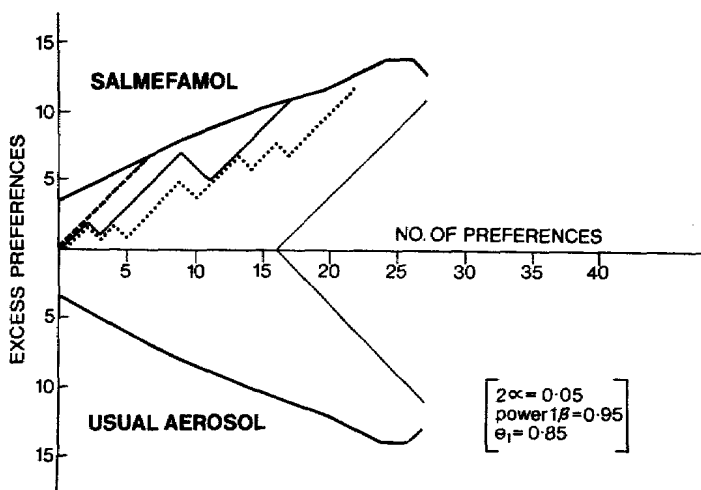


Fig. 3.

Sequential analysis of the data according to the order in which patients entered the trial.

- A — Comparison of mean IMBC (before adrenaline) during salmefamol period with preceding period of usual aerosol.
 B Comparison of mean IMBC (before adrenaline) during salmefamol period with subsequent period of usual aerosol.
 C --- Patients' expressed preference.

period were significantly higher at the 1 per cent level (Table 2 B).

Symptom Scores

Twenty-four patients completed diary cards adequately during the pre-salmefamol period and during the salmefamol period. Symptom scores for the first week of salmefamol were compared with those for the preceding week by Wilcoxon's matched-pairs signed-rank test. Statistically significant improvement occurred in symptoms during the night-time ($P < 0.05$), and during the daytime and the whole 24 hours ($P < 0.01$), upon changing to salmefamol aerosol. Likewise, com-

TABLE 3

Mean Symptom Scores for (A) the 7 Days Immediately Preceding Start of Salmefamol, (B) the First 7 Days of Salmefamol, (C) the Last Week of a 3-Month Period of Salmefamol, and (D) the First Week After Return to Usual Aerosol. (Maximum Possible Scores of 91 for Night or Day Assessments and 182 for Total 24 h Would Indicate Absence of Symptoms).

Week of study	Mean symptom scores		
	Night	Day	Total 24 h
A Usual aerosol just before salmefamol	81.7§	67.5*	149.2*
B Salmefamol aerosol (week 1)	84.6§	71.5*	156.1*
C Salmefamol aerosol (week 13)	81.3	71.2†	152.5
D Usual aerosol just after salmefamol	78.6	69.4†	148.0

§ or † = $P < 0.05$

* = $P < 0.01$

parisons were made between the last week on salmefamol and the following week, but statistical improvement on salmefamol occurred only for daytime scores. There were no statistically significant differences between any of the scores when the first and last weeks of salmefamol therapy were compared (Table 3).

Patients' Preferences

Nineteen patients stated a preference for salmefamol; six for their usual bronchodilator ($P < 0.02$ using chi-squared). When these preferences were plotted on a sequential analysis chart in the order in which the patients entered the trial, a significant result occurred at the 5 per cent level in favour of salmefamol after seven preferences (Fig. 3, line C).

Six patients thought salmefamol acted quicker than their usual aerosol; 15 thought its effect lasted longer; and two slept better. One patient said salmefamol appeared to be "stronger" in its effect.

Side-effects

Five patients had some reaction which they attributed to salmefamol: four developed slight skeletal muscle tremor in

the first few days of treatment, and another a buccal ulcer. No abnormal haematological or biochemical changes were observed at the end of the 3 months' treatment with salmefamol.

One patient showed marked deterioration in his IMBC, coincidentally with the change from his usual aerosol to salmefamol. This may have been drug-related and indicative of idiosyncrasy to the drug. However, on return to his usual aerosol no improvement occurred. The one patient who withdrew from the trial after 3 weeks on salmefamol developed acute asthma.

CONCLUSIONS

The bronchodilator effect of a single dose of salmefamol aerosol has been shown to be of longer duration than other β -stimulant bronchodilators (3, 4). The present investigation, when salmefamol was given four times daily for 3 months, has resulted in the following conclusions:

a) A significant improvement in the ventilatory capacity was sustained in most patients. This improvement was only seen in the pre-adrenaline values, and there was no improvement of post-adrenaline values. In the past, studies have been conducted in a similar way with orciprenaline and salbutamol aerosols, but improvement in pre-adrenaline IMBC has not been noted during treatment with these drugs four times daily for a number of weeks or months (Kennedy, unpublished data).

b) In most patients there was significant symptomatic improvement as judged from the diary scores, and most patients preferred salmefamol to salbutamol or orciprenaline.

c) There was no evidence of tachyphylaxis (diminished broncho-dilator effect) after 3 months' continuous usage.

d) Only minor side effects in the form of slight tremor were occasionally observed. However, two patients deteriorated, and this may be related to drug idiosyncrasy.

e) Treatment with an effective adrenergic bronchodilator not only lessens airway obstruction, but also allows more ef-

fective penetration of other inhalational drugs such as sodium cromoglycate and beclomethasone dipropionate. These three classes of drugs would appear to be mutually supportive in many patients because of their different modes of action.

It would seem, therefore, that salmefamol confers real clinical benefit compared to similar adrenergic compounds, probably because of its longer duration of action; it also has low toxicity and gives rise to only a few minor, and generally transient, side-effects. Nevertheless, not all patients showed improvement; in fact, two actually deteriorated. Whether this is related to idiosyncrasy to the drug or to seasonal influences is uncertain, but it emphasises the need for the judicious use of the many available compounds rather than a habit of 'blanket' prescribing.

SUMMARY

Twenty-five asthmatics were tested with salmefamol aerosol (200 μ g q.d.s.) for a period of 3 months. The ventilatory capacity before and after adrenaline was measured weekly and symptoms were assessed daily using a scoring system over a period of 9 months. The results during the 3 months' treatment with salmefamol were compared with the preceding and succeeding 3-month-periods when patients were receiving either salbutamol aerosol or orciprenaline aerosol. Statistically significant improvements were seen in ventilatory capacity before adrenaline inhalation and in symptom scores while on salmefamol. Ventilatory capacity after adrenaline inhalation remained unchanged throughout the study: thus there was no evidence of tachyphylaxis. A significantly greater number of patients preferred the new drug. Four patients developed slight muscle tremor in the first few days of salmefamol therapy, but there were no changes in haematological or biochemical values after 3 months' therapy. Thus, salmefamol seems to have marked efficacy with low toxicity and is generally well tolerated.

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