INVESTIGATION OF SALBUTAMOL TOLERANCE

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- 1 A double blind cross-over study was carried out on patients with reversible airways disease attending an out-patient clinic.
- 2 Twenty patients were given either salbutamol (200 μ g) or propellant by aerosol for two week periods and in another study twelve patients were given identical tablets containing either salbutamol (4 mg) or placebo for four week periods. Both forms of therapy were taken four times per day but stopped the evening before attending the clinic.
- 3 The improvement in FEV₁ 10 min following salbutamol (200 μ g) by aerosol was measured after previous treatment with either salbutamol or placebo administered by aerosol and orally and the results were compared statistically. This failed to show a significant difference and suggests that regular treatment with salbutamol does not lead to a decreased response.

Introduction

Herxheimer (1946) has shown that tolerance to the bronchodilator action of ephedrine developed over 3-4 days when the drug was given orally three times per day, but took longer to occur if two doses were given daily. It has been assumed that pharmacological tolerance may develop with other bronchodilators when administered regularly (Goodman & Gilman, 1971).

During the last few years salbutamol has become widely used for the relief of bronchospasm (Choo-Kang, Simpson & Grant, 1969). In a double blind cross-over study in patients with chronic asthma treated for four weeks with either placebo or salbutamol, (2 or 4 mg) by mouth, Parker, Choo-Kang, Cooper, Cameron & Grant (1971) found that the larger dose produced significant improvement in the peak flow rate. The increase during the third and fourth weeks was less than that during the second week, although the difference was not statistically significant. They suggested that this slight reduction in peak flow rate during the third and fourth weeks could be due to either the development of drug tolerance or reflect the natural variation in the severity of the asthma. As the development of tolerance could be a limitation to the clinical use of this drug the present study was carried out in patients using salbutamol administered by pressurized aerosol and by mouth to examine the effects of repeated administration.

Method

The study was conducted in two parts in which patients received either a pressurized aerosol or tablets. Patients used for both studies were selected from patients with obstructive airways disease attending the out patient clinic, who were found to have a greater than 10% improvement in the forced expiratory volume at one second (FEV₁), 10 min after two inhalations of salbutamol (200 μ g). The majority of the patients were asthmatics but some also had the symptoms of chronic bronchitis. All were well controlled on bronchodilators and in some instances, corticosteroids (indicated in Tables 1 and 2).

In the first investigation twenty patients were instructed to take two inhalations four times/day for 2 weeks from an aerosol containing either salbutamol (100 μ g/inhalation) or propellant alone, similar to that used in the active aerosol. In the second part of the study twelve patients took salbutamol (4 mg) or identical placebo tablets, four times/day for one month by mouth. Both investigations were conducted in a double blind cross-over fashion with randomization of the treatments. Patients were always given a salbutamol aerosol to use should they develop dyspnoea during the investigations.

Patients taking the aerosol returned to the out-patient clinic after 2 weeks and those taking the tablets returned after 4 weeks. The patients did not take the treatment on the morning on which they were due to attend the hospital. At the out-patient clinic the FEV₁ was measured using a Vitalograph dry spirometer. The mean of three measurements at minute intervals was made. The

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patient was given two inhalations of salbutamol aerosol (200 µg) and 10 min later the FEV₁ was again measured. The patients were then given the alternative treatment, aerosol or tablets to take for a further 2 or 4 weeks after which they returned to the clinic for determination of the response to the inhalation of salbutamol using an identical procedure.

On completion of these studies the responses to the inhalation of salbutamol after administration of the active drug, aerosol or tablets, was compared with the responses determined after the placebo preparation, using the paired *t* test.

Results

The changes in FEV₁ produced by the inhalation of the same dose of salbutamol in twenty patients at the end of 2 weeks treatment with either salbutamol or placebo aerosols are shown in Table 1. There is a marked variation in the response to salbutamol between patients and in the same patient after 2 weeks treatment with salbutamol or propellant. A comparison of the baseline records on the two occasions did not show a significant difference ($P > 0.07$). When the responses to the salbutamol aerosol on the two occasions were compared, no statistically significant difference was found ($P > 0.90$).

The results from the oral study are displayed in Table 2. When the comparison of the increases in FEV₁ after salbutamol aerosol are made in twelve patients after prior treatment with salbutamol tablets (4 mg) four times/day and identical placebo tablets four times/day, no statistically significant difference is detected ($P = 0.4-0.3$). As with the first part of the investigation there is considerable within patient variation in the response to salbutamol inhalations, but there was no significant difference in the baseline recordings ($P > 0.1$).

Discussion

It has been shown by Walker, Evans, Richards & Paterson (1972) that FEV₁ rises to nearly maximum levels within 10 min after inhalation of salbutamol, so that for practical purposes improvement after this time is a suitable measure of response to the drug. A major cause of variation in response to bronchodilator drugs is the initial FEV₁ as Hume & Gandevia (1957) have pointed out. The variation in bronchial tone from day to day and even during the day is pathognomic of bronchial asthma (Howell, 1971), therefore

Table 1 The changes in FEV₁ (ml) following the inhalation of salbutamol (200 µg) after (a) salbutamol aerosol and (b) propellant aerosol

Patients	(a) salbutamol aerosol										(b) propellant aerosol									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
(a) salbutamol (200 µg) by aerosol four times/day for 2 weeks	200	200	150	250	150	150	200	400	317	550	400	400	650	200	0	100	150	0	100	200
(b) propellant aerosol four times/day for 2 weeks	100	300	75	200	0	100	300	450	400	400	100	150	250	150	0	350	150	0	0	750
Differences in FEV ₁ measurements	+100	-100	+75	+50	+150	+50	-100	-50	-83	+150	+300	+250	+400	+50	0	-250	0	0	+100	-550

t Value = 0.0087 for 19 d.f. $P > 0.90$.

* Patients on corticosteroids.

Table 2 The changes in FEV₁ (ml) following the inhalation of salbutamol (200 µg) after (a) salbutamol tablets and (b) placebo tablets

<i>Patients</i>	1	2	3	*	*	6	*	8	*	10	*	*
(a) Salbutamol tablets (4 mg) four times/day for 4 weeks	50	300	100	200	100	100	200	600	400	400	300	400
(b) Placebo tablets four times/day for 4 weeks	200	450	300	150	150	100	250	400	350	700	100	500
Difference in FEV ₁ measurements	-150	-150	-200	+50	-50	0	-50	+200	+50	-300	+200	-100

t Value = 0.9506 for 11 d.f. *P* = 0.4-0.3.

* Patients on corticosteroids.

administration of placebo as part of this double blind study is important.

It was difficult to determine beforehand the duration of such a study. The aerosol study of two weeks was an arbitrary period, while the duration of the tablet study followed the findings of Parker *et al.* (1971), that there was a slight diminution in peak flow rate after 3 to 4 weeks treatment with salbutamol. It could be argued that longer studies may be influenced by the change in season.

The results of this study fail to show that previous treatment with either salbutamol aerosol or tablets in clinically effective doses, produces a statistically significant effect on the FEV₁ improvement after testing with 200 µg by inhalation of salbutamol aerosol. In this clinical study the treatment did not produce any decrease in response.

Drug tolerance or resistance was shown to isoprenaline in relation to the cardiovascular system (Paterson, Connolly, Davies & Dollery, 1968) in asthmatic subjects taking large amounts of isoprenaline by aerosol administration. Tolerance was also demonstrated by Connolly, Davies, Dollery & George (1971) in regard to the dosage of isoprenaline required to increase the pulse rate, to show that there was a significant displacement of the dose-response curve to the

right. A study in guinea pigs by these investigators demonstrated an increased mortality to injected histamine, when the animals had previously received regular injections of salbutamol. A more precise study by Pun, McCullach & Rand (1971) measuring the inflation pressure of the lungs in guinea pigs after injection of histamine, could not show any change in the protection produced by various sympathomimetic amines after either infusion or repeated injections. They conclude that the response to β -receptor stimulating drugs is different in the cardiovascular from the respiratory system, and that no loss in bronchodilator efficacy occurs with repeated administration of the drugs.

A clinical study similar to the present one (Gibson & Tattersfield, 1972) using salbutamol tablets, with regular daily isoprenaline responses, did not exhibit any significant decrease in sensitivity. The information from these clinical studies would confirm some of the experimental evidence that pharmacological tolerance to regular administration of salbutamol either by aerosol or tablets is not found in clinical practice.

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