EVALUATION OF TOLERANCE AFTER CONTINUOUS AND PROLONGED ORAL ADMINISTRATION OF SALBUTAMOL TO ASTHMATIC PATIENTS

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- 1 Salbutamol (8 mg) was administered twice daily as a sustained release formulation to twenty-four asthmatic patients for up to four weeks under double-blind conditions.
- 2 The ability of bronchial smooth muscle to respond was determined by monitoring the response to salbutamol (200 μ g) administered by aerosol at set intervals three times a week.
- 3 There was no evidence of diminishing response during the study period.
- 4 It is concluded that tolerance to salbutamol does not occur at therapeutic dose levels and that clinical observations of tolerance may be due to other factors.

Introduction

Bronchodilators are frequently used in the treatment and management of reversible airway obstruction. Numerous investigators (Choo-Kang, Simpson & Grant, 1969; Parker, Choo-Kang, Cooper, Cameron & Grant, 1971; Cooke, Kerr, Willey, Hoare, Grant & Cameron, 1974) have carried out clinical studies to demonstrate their efficacy and when used appropriately they are generally concluded to be safe. Following the increase in asthmatic death doubts, however, were expressed about their safety on a long term basis and Conolly, Davies, Dollery & George (1971) have suggested that drug induced cross resistance to endogenous sympathomimetic agents can lead to deterioration of the asthmatic state. This study was designed to evaluate whether prolonged exposure to salbutamol administered as a slow-release formulation inhibited the response of bronchial smooth muscle to direct stimulation by salbutamol after intra-bronchial inhalation.

Method

Patients with reversible airway obstruction were suitable candidates for the study. All patients demonstrated a mean minimum improvement of at least 10% in peak expiratory flow rate (PEFR) after inhalation of salbutamol (200 μ g), on three occasions, during the first week of the study. The patients were mainly asthmatic, presenting with

wheezy dyspnoea, but patients with wheezy bronchitis (as shown by the presence of wheeze, cough and dyspnoea) were also included. The aim of the study was carefully explained to each patient and informed consent obtained.

During the first week of the study each patient attended the surgery on Tuesday, Thursday & Saturday. They were instructed in the use of a Wright Peak Flow Meter and their baseline PEFR recorded (highest of three successive attempts). Each patient inhaled two puffs (200 μ g) salbutamol under close supervision and the PEFR recorded 5 and 10 min after inhalation. Only those patients demonstrating a mean minimum increase of at least 10% improvement in PEFR over baseline on the three occasions were included in the study. Twenty-four patients out of thirty patients were suitable and were included in the study. Eight patients received placebo treatment for three weeks, Group A. Eight patients received oral salbutamol treatment for one week, Group B. Eight patients received oral salbutamol treatment for three weeks, Group C. All patients received oral salbutamol in the final week (Week 5), (Table 1). Allocation to treatment was randomized and the study carried out under double-blind conditions.

Each patient recorded his/her response to salbutamol (200 μ g) by aerosol on Tuesday, Thursday and Saturday between 18.00 h and 19.00 h during the next four weeks. (Weeks 1-5

inclusive). The study was designed in this manner to enable a comparison between each group to be made in Week 5. Oral salbutamol treatment during the study period consisted of one salbutamol slow-release formulation administered at 08.00 h and 20.00 hours. Each tablet contained salbutamol (2 mg) in a quick-release layer and salbutamol (6 mg) in a slow-release matrix. Conventional quick-release formulation of salbutamol tablets provides for a total release of active drug in 1 hour. The slow-release formulation was designed to release the total salbutamol content in 6 hours.

Results

Table 2 shows the mean weekly percentage increase in PEFR for each group and the difference in response between the initial pre-study week, (Week 1) and the final week (Week 5). Analysis of variance was carried out on the percentage increases to assess if the response to aerosol challenge diminished when oral salbutamol was administered for one week (Group B) or four weeks (Group C). The differences were not statistically significant ($P > 0.05$). The data was also assessed in terms of response to salbutamol challenges within groups. Figure 1 illustrates the mean response to challenges of salbutamol during the three treatment schedules. There was no significant difference in response irrespective of the treatment period i.e. one week (Group A), three weeks (Group B), or four weeks (Group C).

Figure 1 Mean increase in PEFR to salbutamol (200 µg) in groups of asthmatic patients during treatment with slow-release salbutamol (8 mg, twice a day, ▨) or placebo (□). ▤ pretreatment data.

Discussion

This study was designed to monitor the ability of bronchial smooth muscle to respond under conditions of continuous exposure to salbutamol achieved by administration of oral salbutamol as a slow-release formulation. Darke (personal com-

Table 1 Plan of study

		Week 1	Group	Week 2	Week 3	Week 4	Week 5
			A	Placebo	Placebo	Placebo	Salbutamol
			B	Placebo	Placebo	Salbutamol	Salbutamol
			C	Salbutamol	Salbutamol	Salbutamol	Salbutamol
		↑ ↑ ↑		↑ ↑ ↑	↑ ↑ ↑	↑ ↑ ↑	↑ ↑ ↑
Aerosol salbutamol challenges (200 µg).							

Table 2 Weekly mean % increase in PEFR after inhalation of salbutamol (200 µg).

		1	2	Week 3	4	5	Reduction of % increase 1-5	Difference in means
Group A	PEFR	23.31	21.51	22.23	18.61	16.09		
	Treatment	nil	Placebo	Placebo	Placebo	Salbutamol	7.21%	A-B 8.74%
Group B	PEFR	15.02	19.47	17.44	14.09	16.55		
	Treatment	nil	Placebo	Placebo	Salbutamol	Salbutamol	-1.53%	
Group C	PEFR	19.55	18.71	15.90	13.16	19.27		
	Treatment	nil	Salbutamol	Salbutamol	Salbutamol	Salbutamol	0.28%	A-C 6.93%

munication) demonstrated that the administration of one or two slow-release tablets produced a satisfactory increase in FEV₁ in asthmatic patients for up to 10 h after administration. The ability of the smooth muscle to respond under these conditions was achieved by administration of salbutamol from an aerosol on Tuesday, Thursday & Saturday of each week during the study period and monitoring the response obtained in terms of PEFR. There was no significant difference in magnitude of response, irrespective of the duration of administration. The β_2 -adrenergic receptor in bronchial smooth muscle was always capable of producing similar responses in the presence of exogenous (salbutamol) and endogenous (nor-adrenaline) circulating amines i.e. tolerance did not occur.

Patients in Group C received oral salbutamol for four consecutive weeks. The mean weekly increase in PEFR obtained after administration of 200 μ g salbutamol tended to fall during weeks 2, 3 and 4 but returned to its pre-study level during week five. Parker *et al.* (1971) observed a similar phenomenon after administration of salbutamol (4 mg four times a day) during weeks 3 and 4 of a four week treatment period. In both studies this decrease could represent the natural variations in the disease process or the development of tolerance. In this study the clinical response pattern returned during the fourth treatment week.

Svedmyr, Larsson & Thiringer (1974) infused isoprenaline ($0.1 \mu\text{g kg}^{-1} \text{min}^{-1}$) at monthly intervals to asthmatic patients treated with oral terbutaline for up to three months. Maximum increases in FEV₁ and similar increases in heart rate were obtained after isoprenaline on all occasions confirming that tolerance did not occur. Sims (1974) monitored the response to continuous administration of oral and inhaled salbutamol for four weeks, and concluded that tolerance did not occur. Gibson, Tattersfield & Pride (1972) came to a similar conclusion after administration of oral salbutamol for two weeks and daily challenges with isoprenaline (500 μ g) by inhalation. Smith &

Davies (1973) provided further evidence on an uncontrolled basis in asthmatic patients using salbutamol administered by aerosol for periods of eighteen months. Even under conditions of worsening asthma as suggested by a diminishing baseline in terms of FEV₁, D.H. Smith (personal communication) demonstrated that administration of salbutamol by IPPV always provided similar increases in FEV₁. It appears that the β -adrenoceptor is always capable of stimulation and we conclude that administration of therapeutic doses of salbutamol does not cause tolerance.

Clinical observation of tolerance may be due to other factors. Hume & Gandevia (1957) published data suggesting that the variability in response to isoprenaline is dependant on the baseline pretreatment FEV₁. The response to isoprenaline increased as the baseline FEV₁ decreased from 3 litres to reach a maximum improvement from a baseline FEV₁, 1.0-1.8 litres. The fall in baseline FEV₁ can be considered as uncomplicated asthma due to excess parasympathetic activity only. Further decreases in baseline FEV₁, coinciding with progressively diminishing responses to isoprenaline, are probably due to additional factors e.g. production of mucus, hyperaemia of the bronchial mucosa, presence of infection, etc., a clinical situation requiring treatment with oral or aerosol steroids. Observations of diminishing response under these conditions could be construed as development of tolerance. Alternatively the β_2 -adrenoceptor could become refractory to stimulation under conditions unassociated with excessive use of agonist e.g. Griffin, Kamburoff & Prime (1972) demonstrated improvement in airway conductance in eleven asthmatic patients treated with an α -adrenoceptor blocking drug and orciprenaline, whereas administration of orciprenaline alone had no effect. Diminishing response to bronchodilators in these two situations cannot truly be described as drug tolerance.

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