THE ACUTE EFFECTS OF THE ADMINISTRATION OF RIMITEROL AEROSOL IN ASTHMATIC CHILDREN

MARGARET I. BLACKHALL & BETTY MACARTNEY

Department Child Health, University of Queensland
Medical School, Brisbane 4029, Australia

STELLA R. O'DONNELL

Department Physiology, University of Queensland, Brisbane 4067, Australia

- 1 Ten asthmatic children received on two separate occasions rimiterol (500 μ g) and orciprenaline (1.5 mg) as aerosols in a double-blind, crossover design trial. Respiratory parameters (FEV₁, FVC and PEFR) and pulse rate were recorded for 60 min after each administration.
- 2 Rimiterol produced effective bronchodilation in children with negligible cardiac stimulation. It differed from orciprenaline in that the peak bronchodilator effect was not maintained during the 60 min observation period.
- 3 Rimiterol is a selective, short-acting, sympathomimetic bronchodilator in children.

Introduction

Rimiterol hydrobromide is a β -adrenoceptor stimulant drug which, like isoprenaline, is a catecholamine. However the side chain of the phenylethanolamine structure has been cyclized around the α -carbon atom to form a piperidyl ring. Animal experiments have shown that rimiterol acts selectively on bronchial muscle with less cardiovascular activity (Carney, Daly, Lightowler & Pickering, 1971; Bowman & Roger, 1972; O'Donnell & Wanstall, 1976), and clinical trials in adults (Svedmyr, Malmberg & Thiringer, 1972; Shenfield & Paterson, 1973; Marlin & Turner, 1975) have shown that it is an effective, short-acting, bronchodilator with negligible cardiac effects when given by aerosol. The present study was undertaken to determine the bronchodilator efficacy and cardiac effects of rimiterol aerosol in asthmatic children and to compare these in a double-blind study, with the effects of orciprenaline aerosol which was one of the drugs in use at that time in the Royal Children's Hospital, Brisbane.

Methods

Subjects

The asthmatic children in the study were aged between 7 and 14 years, had reversible airways obstruction and were able reliably to perform respiratory function tests. They were accepted for study only if their forced expiratory volume in the first second (FEV₁) was at

least 2 standard deviations (s.d.) below their predicted normal value according to Strang (1959), and all children were in a symptom free period between attacks. Informed consent was always obtained from the child's parents and the study was approved by the appropriate authorities of the hospital. All bronchodilator drugs were withheld for a minimum of 9 h before the study but disodium cromoglycate and/or steroid therapy was continued

Design of study

Initially ten children (eight male, two female) received rimiterol (500 μ g) given as two 250 μ g puffs in order to establish that the manufacturer's recommended dose was effective and safe in children.

A double-blind, crossover design, comparison of rimiterol with orciprenaline was then carried out in a further group of ten children (five males, five females). All children received rimiterol (500 μ g as two puffs) on one occasion and orciprenaline (1.5 mg given as two puffs of 750 μ g) on the other occasion. Since the canisters were slightly different in size, even though the mouthpieces were the same, drugs were administered by the Medical Practitioner so that neither the technician making all the readings nor the patient knew which drug had been administered. The drugs were administered at the same time of day on both occasions but the second treatment was given only when the patient presented with an FEV₁ within 15% of that at the first treatment.

Figure 1 Mean increases in FEV₁ and FVC and actual PEFR and pulse rate readings at various time intervals after administration at time 0 of either 2 puffs (500 µg) rimiterol aerosol (●) or 2 puffs (1.5 mg) orciprenaline aerosol (○). Points represent mean results from a group of ten children given both drugs and bars represent s.e. means.

Experimental procedure

After the patient had rested for at least 10 min, pulse rate was counted for 30 s. Basal measurements of FEV₁ and forced vital capacity (FVC), using a dry spirometer (Vitalograph) and of peak expiratory flow rate (PEFR), using a Wright's peak flow meter, were then made. Two puffs of the inhaler designated for that day were given, the canisters being weighed before and after drug administration to determine the amount of drug expelled and therefore ensure that the aerosols triggered properly. Thereafter recordings of pulse rate, FEV₁, FVC and PEFR, repeated in that order, were made at 2, 6, 10, 15, 20, 30, 45 and 60 min. The peak values of FEV₁, FVC, PEFR and pulse rate after treatment were noted. All volumes measured at ATPS were converted to BTPS using appropriate conversion factors. All statistical comparisons have been carried out using a *t*-test on paired values.

Results

The mean age of the ten children in the double-blind study on rimiterol and orciprenaline was 10.4 ± 0.6 years (range 7.0–14.0) and the mean height was 138.3 ± 3.9 cm (range 122.4–156.5). The mean results from the study are summarized in Table 1 and

Figure 1. All the mean pretreatment (basal) values for respiratory function tests are significantly less than mean predicted values ($P < 0.001$) and the mean pretreatment values on the two occasions on which the children were given drugs are not significantly different. Rimiterol (500 µg) and orciprenaline (1.5 mg) both caused significant improvement in FEV₁, FVC and PEFR, i.e. peak values were significantly increased compared with basal values (Table 1: rimiterol (d.f.9); FEV₁ $t = 8.09$, $P < 0.001$; FVC $t = 3.77$, $0.01 > P > 0.001$; PEFR $t = 6.66$, $P < 0.001$; orciprenaline (d.f.9); FEV₁ $t = 12.22$, $P < 0.001$; FVC $t = 5.61$, $P < 0.001$; PEFR $t = 10.36$, $P < 0.001$). There was no significant difference between the maximum increases in FEV₁, FVC and PEFR seen after the two drugs (Table 1). In Figure 1 the mean responses of the group obtained at the various time intervals are plotted and this illustrates that for both drugs the improvement in respiratory function was quick in onset in that FEV₁, FVC and PEFR were all significantly increased 2 min after administration. For both drugs, improvement was still maintained at 15 min and, until 45 min, there was no significant difference between the responses to rimiterol and orciprenaline. However, with rimiterol the responses gradually declined from 15 min after treatment and by 60 min, although the respiratory function readings were still significantly ($P < 0.05$) increased compared with basal values, they were

Figure 2 Mean increases in FEV₁, FVC, actual PEFR and pulse rate readings at various time intervals after 2 puffs rimiterol aerosol (500 µg) given at time 0. Points represent mean results from a group of 20 children and bars represent s.e. means.

significantly ($P < 0.05$) less than those obtained immediately after rimiterol. The effects of orciprenaline were maintained over the 60 min observation resulting in a significantly greater increase in FEV₁ at 60 min after orciprenaline than at 60 min after rimiterol ($t = 3.16$, $0.02 > P > 0.01$). Six of the ten children had values for FEV₁ at 60 min close to basal levels after rimiterol whereas all ten children had levels at least 200 ml above basal readings after orciprenaline.

Pulse rate was monitored in all children and this

showed no significant change over the 60 min period for either drug (Figure 1). For both drugs there was a small but not significant difference between the mean pretreatment value of pulse rate and the mean peak value after the drug (Table 1; rimiterol, $t = 2.1$; orciprenaline, $t = 2.1$) and there was no difference between the two drugs in this regard.

Since an additional ten children had received rimiterol in the pilot study prior to the double-blind trial, the mean results for the total of twenty children (thirteen male, seven female) who received a single

Table 1 Respiratory function and pulse rate readings (mean values $\pm$ s.e. mean) ($n = 10$) for a group of children receiving 500 µg rimiterol aerosol and 1.5 mg orciprenaline aerosol in a double-blind trial

		Rimiterol	Orciprenaline
FEV ₁ (l) (Predicted 2.14 ± 0.16)	Basal	1.45 ± 0.14	1.49 ± 0.12
	Peak	1.82 ± 0.15	1.95 ± 0.12
	Maximum increase	0.37 ± 0.05	0.46 ± 0.04
FVC (l) (Predicted 2.42 ± 0.18)	Basal	2.02 ± 0.19	2.05 ± 0.12
	Peak	2.26 ± 0.22	2.38 ± 0.18
	Maximum increase	0.24 ± 0.06	0.33 ± 0.06
PEFR (l/min) (Predicted 298.0 ± 18.2)	Basal	207 ± 24.8	229 ± 20.1
	Peak	276 ± 20.6	299 ± 20.3
	Maximum increase	69 ± 32.9	70 ± 6.8
Pulse rate (beats/min)	Basal	97.8 ± 5.3	94.2 ± 4.5
	Peak	103.4 ± 6.4	98.4 ± 4.5

administration of rimiterol aerosol during this study have been combined and are illustrated in Figure 2.

Discussion

In the present study administration of rimiterol aerosol in a dose of 500 µg and orciprenaline aerosol in a dose of 1.5 mg produced equieffective bronchodilation in a group of asthmatic children with reversible airways obstruction. Neither drug produced significant effects on the pulse rate. The small changes which did occur in some children on both drugs were probably unrelated to drug therapy since comparable increases in pulse rate have been shown to occur even with placebo aerosols (Choo-Kang, Simpson & Grant, 1969). The two aerosols differed in that the effects of rimiterol started to decline 15 min after administration whereas those of orciprenaline were maintained during the 60 min observation period. This probably reflects the more rapid metabolism of rimiterol, probably directly in the lung (Shenfield, Evans & Paterson, 1976), since rimiterol is a catecholamine which can be attacked by catechol-O-methyltransferase. Orciprenaline is not broken down by degradative enzymes (Dengler & Hengstmann, 1976).

Thus both rimiterol and orciprenaline showed bronchodilator selectivity when used as aerosols in children, even though orciprenaline has been shown to be less β_2 -selective than rimiterol in pharmacological

studies (O'Donnell & Wanstall, 1974, 1976). The short duration of action of rimiterol raises the question of whether it is a desirable property or not in β_2 -selective stimulant drugs. A number of clinical situations can be envisaged where it could be useful. Prolonged bronchodilation is not required in the laboratory assessment of the reversibility of airways obstruction in children and the selectivity of rimiterol's action makes it preferable to the alternative short-acting, non-selective drug, isoprenaline. In the long-term treatment of asthmatic children the combination of a short-acting selective β -adrenoceptor stimulant such as rimiterol with, for example, a theophylline compound, could provide an alternative to the use of a long-acting β -adrenoceptor stimulant. In the treatment of status asthmaticus using intermittent positive pressure ventilation (Cooke, Kerr, Willey, Hoare, Grant & Crompton, 1974) or in inhalation therapy using, for example, a Wright's nebulizer, the short duration of action of rimiterol may be an additional safety factor in that, if it should be necessary to withdraw therapy, the effects of the drug would be more readily reversed. A similar situation would apply to the use of this drug by the intravenous route.

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