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Effects of xamoterol (ICI 118,587) in asthmatic patients

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1 To study the cardioselectivity of xamoterol, eight asthmatic patients took part in a randomised, double-blind, cross-over study, in which xamoterol or saline were infused, followed by four increasing doses of terbutaline i.v.

2 Circulatory studies showed a significant increase of systolic blood pressure after xamoterol 0.1 mg/kg compared to saline ($P < 0.05$), and heart rate tended to increase. Diastolic blood pressure did not show any significant changes after the different treatments.

3 Skeletal muscle tremor measurements with terbutaline stimulation did not show any differences after pre-treatment with either xamoterol or saline.

4 Mean values of FEV_1 did not reveal any significant difference before or after terbutaline stimulation between xamoterol and saline pre-treatments. However, in one patient, FEV decreased 60% after xamoterol, an effect which was reversed by terbutaline.

5 Xamoterol did not have any effect on β-adrenoceptor mediated skeletal muscle tremor and no significant effect on β-adrenoceptor mediated bronchodilation in doses which gave a significant increase of systolic blood pressure. Thus, xamoterol was shown to be a selective β_1-adrenoceptor agonist in man.

Keywords xamoterol terbutaline asthma β-adrenoceptors cardioselectivity

Introduction

Xamoterol (ICI 118,587) has, in animal experiments, been shown to be a β_1-adrenoceptor partial agonist with about 43% of the maximum effect of isoprenaline with no agonist effect at the β_2-adrenoceptor. Xamoterol does however combine with β_2-adrenoceptors as demonstrated by the competitive inhibition of the effects of isoprenaline and as an antagonist of isoprenaline, the xamoterol is 13 times more potent at the β_1- than the β_2-adrenoceptor (Nuttall & Snow, 1982).

In man xamoterol has been shown to have modest β_1-adrenoceptor stimulating effects and to be of benefit in the treatment of heart failure, both in acute studies and after prolonged treatment (Rousseau *et al.*, 1983; Rousseau & Pouleur, 1983; Molajo *et al.*, 1983; Simonsen, 1982; Mancia *et al.*, 1982). The β_1-adrenoceptor antagonistic effects have been demonstrated as a reduction in exercise heart rate, occurring only during moderate to severe exercise when the heart rate is in excess of 120 beats/min (Harry *et al.*, 1981).

Therefore, it is considered important to further evaluate the selectivity of xamoterol in man, and in particular in asthmatic patients, in whom both β_1- and β_2-adrenoceptor effects may be more easily demonstrated (Löfdahl, 1982).

Methods

Experimental design

The study was a double-blind, randomised cross-over comparison in stable intrinsic asthmatic patients, to whom intravenous injections

of xamoterol or saline were given, followed by four intravenous injections of terbutaline. The experiment was concluded by inhalation of terbutaline from a metered aerosol.

The design of the study was approved by the Ethical Committee of the University of Göteborg.

Patients

Nine patients with intrinsic asthma were included in the study. One patient who did not respond to terbutaline on either placebo or xamoterol treatment was excluded from calculations. The remaining eight patients are presented in Table 1. They had a reversibility of FEV_1 of 21–50% after five inhalations of terbutaline sulphate (1.25 mg). If the difference of basal FEV_1-values between the days of examination was above 15%, the experiment was repeated compromising the order of examination according to randomisation in one patient.

The study was performed when the patients were in a stable phase. Previous drug treatments are listed in Table 1. During the study β_2-adrenoceptor agonists were withdrawn 12 h before each experiment. Theophylline therapy was stopped 36 h before the trial. Patients on corticosteroid therapy continued their therapy unchanged during the study.

Experimental details

The patients arrived at the laboratory at 07.30 h after a light breakfast, without coffee or tea. An intravenous catheter was inserted in a superficial arm vein. The patient rested comfortably in a semi-recumbent position for 60 min and then basal measurements were performed. During the whole experiment the patients were seated in a semi-recumbent position. Measurements were made in the following order:-

(1) Heart rate from a continuous ECG recording.
(2) Blood pressure by the cuff method.
(3) Skeletal muscle tremor by a single plane accelerometer according to the method of Thiringer & Svedmyr (1975). The tremor ratio was calculated as the amplitude after the respective treatment divided by the control amplitude before any treatment.
(4) FEV_1 (forced expiratory volume in 1 s) and FVC (functional vital capacity) were measured with a Colin's Survey spirometer. Two measurements of FEV_1 were made and the highest was used for the calculations.

After basal measurements, xamoterol or placebo was infused for 6 min. The xamoterol dose was 0.1 mg/kg. Heart rate was measured also during the last 30 s of infusion.

Terbutaline was then given intravenously in four increasing doses 30-120 min after the start of the xamoterol infusion. Terbutaline was infused for 6 min and the interval between infusions was 30 min. The doses given were 0.22, 0.70, 2.3 and 7.4 μg/kg i.v. All measurements were repeated 15 min after the start of the infusion of xamoterol or control.

Twenty minutes after the last terbutaline infusion the patient inhaled six puffs of terbutaline (Bricanyl®, Draco) from a metered aerosol, and 5 min later all measurements were repeated. The inhalation was carefully supervised, and the patients well-trained in inhalation technique.

Statistical methods

Results are shown as mean ± s.e. mean. Student's *t*-test for paired comparisons was used

Table 1 Clinical details on patients

	Age (years)	*Sex*	*Height (cm)*	*Weight (kg)*	*Diagnosis*	*FEV_1 (1) before study*	*Reversibility %*	*Previous drug treatment*
1	70	M	178	69	A + C	1.30	27	O B, I B
2	63	M	186	70	A	1.90	21	I B, I C
3	50	M	185	113	A	2.40	37	I B, O B, I C, O T, O C
4	60	M	178	85	A	1.10	50	O T, I B, I C
5	59	M	180	94	A + C	1.50	47	O T, I B, I C
6	43	F	157	50	A + C	1.50	44	O T, I B, I C, I A
7	65	M	168	80	A	0.80	43	I B, O T
8	51	M	176	52	A	1.30	47	I B

A = Asthma, C = chronic bronchitis
O = Oral, I = inhaled
A = Anticholinergic, B = β_2-adrenoceptor stimulant, C = Corticosteroid, T = Theophylline

for the calculation of the significance of differences.

Results

Respiratory studies Figure 1 (a and b)

There was no significant difference between xamoterol or saline pre-treatment on the response of the FEV_1 to terbutaline infusion and inhalation. One patient showed a very large decrease (about 60%) after xamoterol, but no significant change after saline (patient 2, Figure 1). This patient was studied twice with xamoterol because of basal value variation, and both times his FEV_1 fell to the same level, an effect which was reversible by terbutaline. Another patient's FEV_1 decreased 28% after xamoterol and 11% after saline. FVC measurements showed similar effects as FEV_1.

Systolic blood pressure (Figure 2)

Systolic blood pressure was 10 ± 3 mm Hg ($P < 0.05$) higher 15 min after xamoterol than after saline. There was also a tendency towards higher values during the terbutaline infusions.

Diastolic blood pressure

Terbutaline caused a dose dependent fall in diastolic blood pressure which was not altered in the presence of xamoterol.

Heart rate (Figure 3)

There was a tendency ($P < 0.1$) for a small increase in heart rate after xamoterol (6 ± 3 beats/min). However xamoterol did not affect the increase in heart rate brought about by the highest infusion of terbutaline.

Skeletal muscle tremor (Figure 4)

There was no significant differences after xamoterol or saline treatment to the increase in muscle tremor brought about by terbutaline.

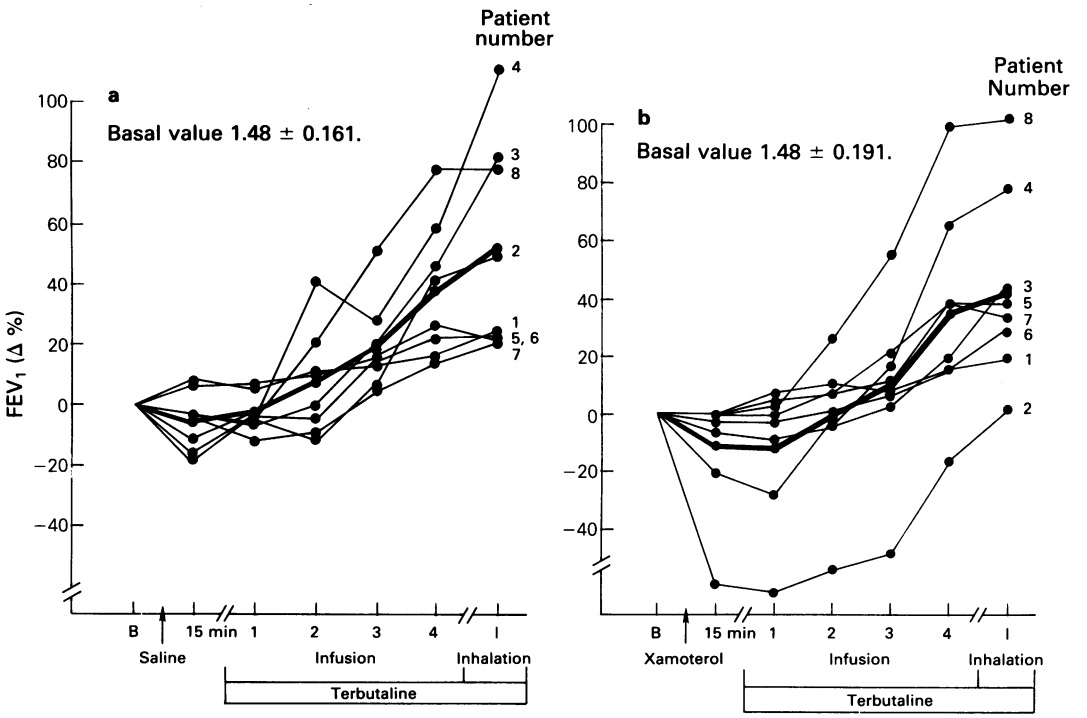

Figure 1 Mean (thick lines) and individual changes in FEV_1, produced by terbutaline (1, 0.22; 2, 0.70; 3, 2.3; 4, 7.4 μg/kg i.v. and inhalation I 1.5 mg) (a) after saline and after (b) xamoterol (0.1 mg/kg i.v.). B, basal value.

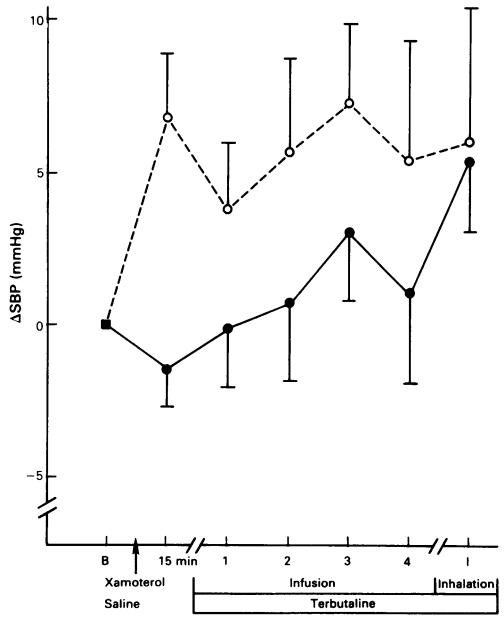

Figure 2 Mean (± s.e. mean) effects on eight patients on systolic blood pressure of terbutaline (1, 0.21; 2, 0.70; 3, 2.3; 4, 7.4 μg/kg i.v. and inhalation 1.5 mg) in the presence of xamoterol (0.1 mg/kg i.v.) and saline. B, basal before xamoterol 127 ± 5 mm Hg and before saline 129 ± 5 mm Hg.

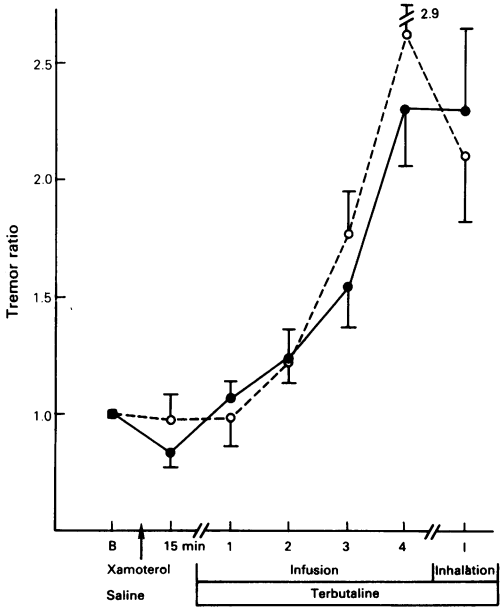

Figure 4 Mean (± s.e. mean) skeletal muscle tremor ratio, relative to basal value (B) of one in eight patients; effects of terbutaline (1, 0.22; 2, 0.70; 3, 2.3; 4, 7.4 μg/kg i.v. and inhalation 1.5 mg) in the presence of xamoterol (○, 0.1 mg/kg i.v.) and saline (●).

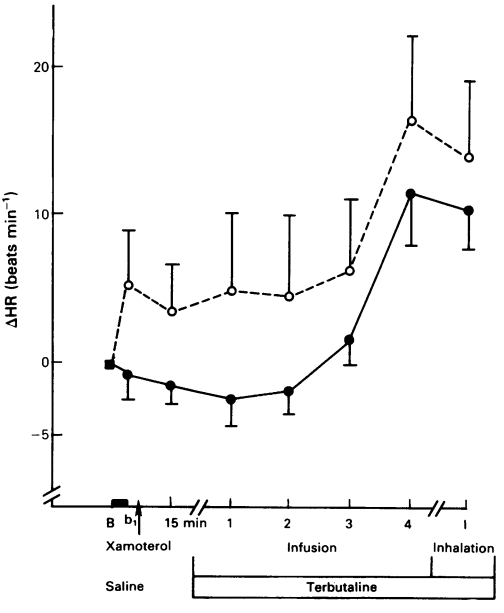

Figure 3 Mean (± s.e. mean) effects in eight patients on heart rate of terbutaline (1, 0.22; 2, 0.70; 3, 2.3; 4, 7.4 μg/kg i.v. and inhalation 1.5 mg) in the presence of xamoterol (○, 0.1 mg/kg i.v.) and saline (●). B, basal before xamoterol 62 ± 2 beats/min and before saline 63 ± 2 beats/min.

Discussion

In the present study in man, the β_1-adrenoceptor stimulating effects of xamoterol were indicated by an increase in systolic blood pressure, no change in diastolic blood pressure and a tendency to increase heart rate (approximately 6 beats/min). The absence of an effect of xamoterol on either FEV_1, skeletal muscle tremor or diastolic blood pressure is consistent with the lack of β_2-adrenoceptor stimulating properties demonstrated in the dog (Nuttall & Snow, 1982). Furthermore, the ability of terbutaline to increase FEV_1, skeletal muscle tremor and reduce diastolic blood pressure was not prevented by prior treatment with xamoterol at a dose of 100 μg/kg i.v., a dose which produces maximum β_1-adrenoceptor stimulating effects (Bobik *et al.*, 1983).

Thus, it seems probable that xamoterol in this dose is less β_2-adrenoceptor antagonistic than atenolol or metoprolol, which have given significant effects in a similar study (Löfdahl & Svedmyr, 1981). However, one patient had a substantial decrease of FEV_1 after xamoterol which was reversed by terbutaline. This patient has, in several studies, been shown to be very susceptible to β_2-adrenoceptor blockade

(Löfdahl & Svedmyr, 1982; Löfdahl *et al.*, 1983).

It may be concluded that in the majority of patients with stable intrinsic asthma so far studied, xamoterol has little or no β_2-adrenoceptor antagonist effect. However, it seems advisable to use with care even a selective β_1-adrenoceptor drug such as xamoterol as occasionally asthmatic patients are encountered in whom bronchoconstruction, reversible by terbutaline, may be caused.

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