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A comparative study on the ventilatory and haemodynamic effects of xamoterol and atenolol in asthmatic patients

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1 The effects of single oral doses of atenolol 50 mg and xamoterol 200 mg (a recently developed partial β_1-adrenoceptor agonist) on lung function, heart rate and blood pressure were investigated in 11 patients with asthma.
2 Xamoterol caused a significant increase in heart rate and systolic blood pressure, which changes are consistent with the partial β_1-adrenoceptor agonist activity of this drug.
3 Atenolol induced a significant decrease in FEV_1 and the forced vital capacity (FVC); there was a non-significant change in FEV_1 and FVC after xamoterol. There was no significant difference between the effects of atenolol and xamoterol on FEV_1 and FVC.
4 Bronchospasm induced by atenolol 50 mg and xamoterol 200 mg was completely reversed by inhalation of the β_2-adrenoceptor agonist terbutaline to a cumulative dose of 4.0 mg.

Keywords asthma atenolol xamoterol β_1-adrenoceptor function

Introduction

Soon after the introduction of nonselective β-adrenoceptor antagonists it became clear, that these drugs can induce severe bronchospasm in asthmatic patients (McNeill, 1964). The introduction of β_1-adrenoceptor selective antagonists seemed to be an advantage, but this type of drug can also induce bronchoconstriction in some asthmatic patients (Greefhorst & Van Herwaarden, 1981; Lammers *et al.*, 1984; Ellis *et al.*, 1981). The decline in lung function after a β_1-adrenoceptor-selective blocker can be explained via two possibilities: β_1-adrenoceptor selectivity is a relative characteristic: increasing the dose leads to a decrease in selectivity (Fleming *et al.*, 1978). Another possibility is that there are apart from β_2-adrenoceptor also β_1-adrenoceptors in the airways by which bronchodilatation is mediated. *In vitro* experiments have demonstrated that the ratio of β_2- to β_1- adrenoceptors varies between species (Rugg *et al.*, 1978). Zaagsma *et al.* (1983), however, could only demonstrate a homogeneous β_2-adrenoceptor population in human tracheal and bronchial smooth muscle. Results of experiments in asthmatic patients with prenalterol, a partial β_1-adrenoceptor agonist, are conflicting. Löfdahl & Svedmyr (1982) could not demonstrate a bronchodilator effect of prenalterol in asthmatics, whereas Greefhorst & Van Herwaarden (1983) were able to demonstrate an increase in vital capacity after prenalterol in asthmatic patients. Xamoterol (ICI 118, 587) is a β_1-adrenoceptor antagonist with substantial partial β_1-adrenoceptor agonist activity (Nuttall & Snow, 1982; Rousseau *et al.*, 1983). In animal experiments xamoterol was shown to exhibit a higher β_1-adrenoceptor selectivity than prenalterol (Cook *et al.*, 1984). It seemed therefore of interest to investigate if the β_1-adrenoceptor agonist activity of xamoterol has an effect on the lung function of asthmatic patients. The effects of xamoterol on lung function, heart rate and blood pressure were compared with those of the β_1-adrenoceptor antagonist atenolol on these parameters. We

also investigated the interaction of both drugs with the bronchodilator effect of the β_2-adrenoceptor agonist terbutaline.

Methods

Eleven male patients with bronchial asthma (American Thoracic Society, 1962) completed the study. Some clinical details are given in Table 1. Their mean age was 36.6 years, their mean height 176.9 cm and their mean weight 73.7 kg. Five of them were cigarette smokers, the others being nonsmokers. There were seven patients with atopic extrinsic asthma with one or more positive skin tests to inhalational allergens. None of the patients suffered from cardiovascular diseases. Their ventilation was moderately to mildly disturbed: the forced expiratory volume in one second (FEV_1) ranged from 40 to 74% of the predicted normal value (Quanjer, 1983). In all patients FEV_1 increased 15% or more after stimulation with a β_2-adrenoceptor agonist. Bronchodilator medication was stopped at least 12 h before the start of the first measurement on each study day. Cromoglycate and beclomethasone were not inhaled on the days of investigation. All patients refrained from smoking and drinking caffeine containing beverages 24 h before each study period. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient before entry into the study.

The investigations were performed on three different days. Placebo was given single-blind on the first day. On the 2 other days the patients received double-blind and in random order xamoterol 200 mg and atenolol 50 mg. Between the study days 2 and 3 there was an interval of at least 4 days to serve as a washout period. All measurements started at noon to minimize the effects of diurnal rhythm in airway conductance which frequently occurs in asthmatics (Connolly, 1979). The study drugs were administered orally before a standard meal to avoid differences in bioavailability within each subject (Melander *et al.*, 1977).

Before and 2 h after drug intake the following measurements were performed after a resting period of at least 30 min: forced vital capacity (FVC), FEV_1 and peak expiratory flow rate (PEFR) were derived from maximal expiratory flow-volume curves which were measured with a Fleischenr 4 pneumotachograph. Heart rate (HR) was recorded with an electrocardiograph (Hellige) and blood pressure (BP) was assessed with the cuff-method (mean of 2 readings; Korotkoff phase 5). The values of the measurements obtained before drug intake are referred to as baseline values. Subsequently, dose-response curves with a β_2-adrenoceptor agonist were performed by assessing HR, BP and flow-volume curves 15 min after inhalation of increasing doses of terbutaline. Terbutaline was administered with a metered dose inhaler in cumulative doses of 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg. In order to facilitate inhalation, terbutaline was inhaled through a Nebuhaler® (Astra), being a cone-shaped extension device of 750 ml (Newman *et al.*, 1981). The results are presented as mean ± s.e. mean. For statistical analysis the Wilcoxon test for paired observations was used. Comparisons were made between baseline values and the values 2 h after drug intake and the latter values were also compared with the values after inhalation of terbutaline. Furthermore, the effects of xamoterol and atenolol were compared with each other and with placebo. Statistical significance was defined as $P<0.05$ (Colton, 1974).

Results

No significant differences were found between the baseline values of the indices measured on the different days of the study. The effects of xamoterol and atenolol on the baseline values of HR and BP are shown in Figure 1 (upper panel). HR increased significantly by 10.8 ± 2.1 beats min^{-1} ($P<0.01$) 2 h after intake of xamoterol and decreased significantly by 9.4 ± 1.5 beats min^{-1} ($P<0.01$) after atenolol as compared to the baseline values of the same day. Two hours post-dose xamoterol caused an increase in systolic BP of 7.4 ± 2.0 mmHg ($P<0.01$), whereas after atenolol systolic BP decreased by 8.3 ± 1.5 mmHg ($P<0.01$). All three study drugs caused a significant fall in diastolic BP. The decline in diastolic BP after xamoterol and atenolol did not differ significantly from the effect of placebo on this parameter.

The changes in lung function parameters 2 h after drug intake, as compared to the baseline values of the same day, are presented in Table 2 and Figures 1 (lower panel) and 2. Atenolol caused a mean decrease in FVC of 0.35 l and in FEV_1 of 0.35 l, both changes being significant. There was a tendency towards a decrease in mean FVC and FEV_1 during xamoterol, but this mean change was not significant. The effect of xamoterol on FVC and FEV_1 was caused by a decrease of more than 10% in baseline values in three of 11 patients, as is shown for FEV_1 in Figure 2. Atenolol, however, induced in seven

Table 1 Patient characteristics

Subject	Age (years)	Smoking history	Asthma type*	Height (cm)	Weight (kg)	FEV_1 actual (1)	FEV_1 % of predicted values	FEV_1 % increase with terbutaline	Therapy**
1	58	+	I	161	68	1.50	55	30	-
2	47	−	I	182	94	2.68	68	25	B S
3	32	−	I	188	74	3.40	74	19	-
4	25	−	E	171	66	1.70	40	29	S
5	24	+	E	178	61	2.60	57	29	-
6	43	+	E	178	92	2.25	58	18	B S
7	38	−	E	169	54	1.70	47	50	C S
8	22	−	E	180	63	2.60	58	35	S
9	60	+	I	174	80	2.28	70	15	S
10	23	−	E	185	78	3.70	74	24	S
11	31	+	E	180	81	2.50	57	44	S
mean ±s.e. mean	36.6 ± 4.2			176.9 ± 2.3	73.7 ± 3.8	2.45 ± 0.2	59.8 ± 3.3	28.9 ± 3.2	

* E = extrinsic; I = intrinsic
**B = beclomethasone; C = cromoglycate; S = salbutamol
FEV_1 = forced expiratory volume in one second (1)

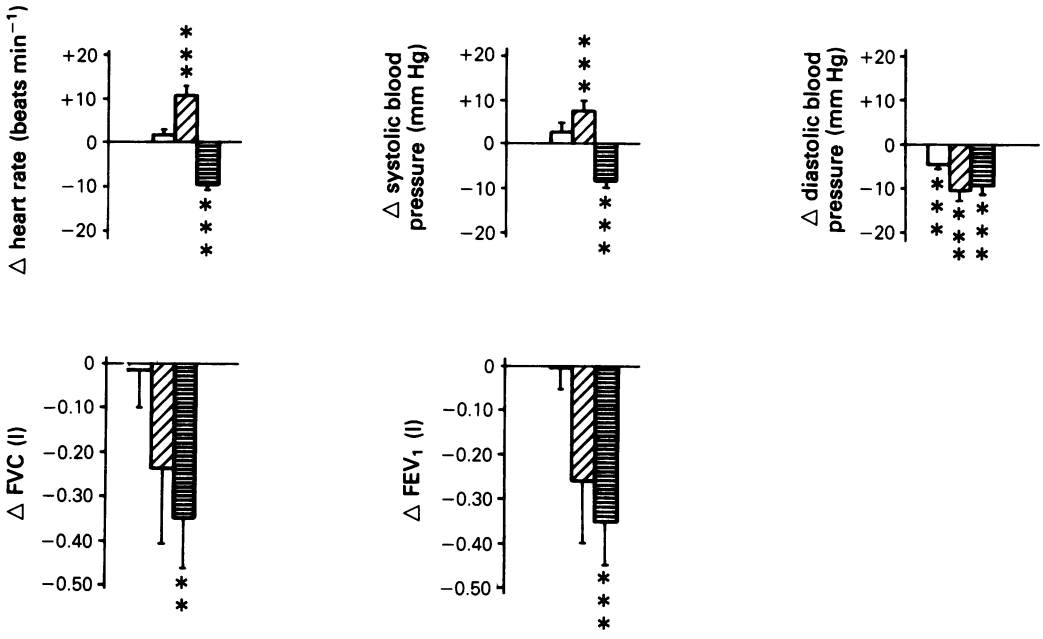

Figure 1 Changes in haemodynamic and ventilatory indices 2 h after intake of placebo (□), xamoterol 200 mg (▨) and atenolol 50 mg (■), as compared to baseline values (mean ± s.e. mean). * $P<0.05$; ** $P<0.02$; *** $P<0.01$.

of the 11 patients such a decrease in FVC and FEV_1. There was no significant difference between the effects of xamoterol and atenolol on FVC and FEV_1 2 h after dug intake. The PEFR did not change significantly after placebo, xamoterol and atenolol.

Inhalation of terbutaline up to a cumulative dose of 4.0 mg had no effect on HR or systolic BP. Also diastolic BP did not change after terbutaline during placebo. However, diastolic BP did increase significantly after 4.0 mg terbutaline during atenolol by 7.1 ± 3.1 mmHg ($P<0.02$) and during xamoterol by 9.9 ± 2.2 mmHg ($P<0.01$).

The effects of terbutaline on lung function are shown in Table 2 and Figure 3. A significant improvement in FVC, FEV_1 and PEFR was found during placebo, atenolol and xamoterol. Comparison of the increases in FVC and FEV_1 by terbutaline did not reveal significant differences between placebo, atenolol or xamoterol (Figure 3). However, after maximal stimulation with terbutaline the absolute FEV_1 values during placebo were significantly higher than the absolute FEV_1 values after atenolol ($P<0.02$) and after xamoterol ($P<0.05$). There was no such significant differences between xamoterol and atenolol (Table 2).

Discussion

The purpose of this study was to investigate the effects of xamoterol, a partial β_1-adrenoceptor agonist (Nuttall & Snow, 1982; Rousseau *et al.*, 1983) on lung function, HR and BP in comparison with placebo and atenolol, a β_1-adrenoceptor-selective antagonist (Ellis *et al.*, 1981; Lammers *et al.*, 1985). Xamoterol acts as a β-adrenoceptor agonist at low levels of sympathetic tone, but as a β-adrenoceptor antagonist when sympathetic tone is high, as during exercise (Harry *et al.*, 1981; Rousseau *et al.*, 1983; O'Neill *et al.*, 1984). As we were interested to see whether xamoterol had any effect on lung function in view of its intrinsic sympathomimetic activity, the patients were studied at rest. The study was performed in asthmatic patients with a reversibility of their FEV_1 of at least 15%, because these patients are more susceptible to the bronchoconstrictor effects of β-adrenoceptor antagonists than

Table 2 Ventilatory parameters before and after intake of placebo, atenolol and xamoterol and after cumulative doses of terbutaline (mean ± s.e. mean)

					Values after inhalation of terbutaline							
		Baseline values	*Values 2h after drug intake*	P*	*0.5mg*	P⁺	*1.0mg*	P⁺	*2.0mg*	P⁺	*4.0mg*	P⁺
FVC(1)												
Placebo		4.58 ± 0.31	4.56 ± 0.28	NS	4.85 ±0.30	NS	5.01 ± 0.30	<0.02	5.05 ± 0.27	<0.01	5.11 ± 0.30	<0.01
Atenolol	50mg	4.58 ± 0.29	4.24 ± 0.30	<0.02	4.66 ± 0.28	<0.01	4.79 ± 0.29	<0.01	4.95 ± 0.28	<0.01	5.00 ± 0.28	<0.01
Xamoterol	200mg	4.60 ± 0.27	4.35 ± 0.32	NS	4.72 ± 0.32	<0.01	4.84 ± 0.32	<0.01	5.31 ± 0.31	<0.01	5.05 ± 0.32	<0.01
$FEV_1(1)$												
Placebo		2.89 ± 0.27	2.88 ± 0.28	NS	3.17 ± 0.32	<0.05	3.43 ± 0.31	<0.01	3.59 ± 0.31	<0.01	3.74 ± 0.31	<0.01
Atenolol	50 mg	2.84 ± 0.30	2.49 ± 0.28	<0.01	2.95 ± 0.33	<0.01	3.12 ± 0.34	<0.01	3.33 ± 0.34	<0.01	3.37 ± 0.34	<0.01
Xamoterol	200 mg	2.95 ± 0.24	2.69 ± 0.31	NS	3.04 ± 0.36	<0.01	3.23 ± 0.36	<0.01	3.45 ± 0.35	<0.01	3.53 ± 0.35	<0.01
PEFR ($1s^{-1}$)												
Placebo		6.95 ± 0.64	7.13 ± 0.72	NS	8.04 ± 0.75	<0.02	8.52 ± 0.78	<0.01	9.01 ± 0.76	<0.01	9.37 ± 0.91	<0.01
Atenolol	50 mg	7.36 ± 0.72	6.84 ± 0.75	NS	7.97 ± 0.89	<0.05	7.85 ± 0.98	NS	9.06 ± 0.87	<0.01	9.14 ± 0.90	<0.01
Xamoterol	200 mg	7.98 ± 0.81	6.83 ± 0.73	NS	7.76 ± 0.94	<0.05	8.42 ± 1.00	<0.01	8.99 ± 0.90	<0.01	9.14 ± 0.88	<0.01

*P**: values 2h after drug intake *vs* baseline values.
P⁺: values after inhalation of terbutaline *vs* values 2 h after drug intake.
NS: not significant.

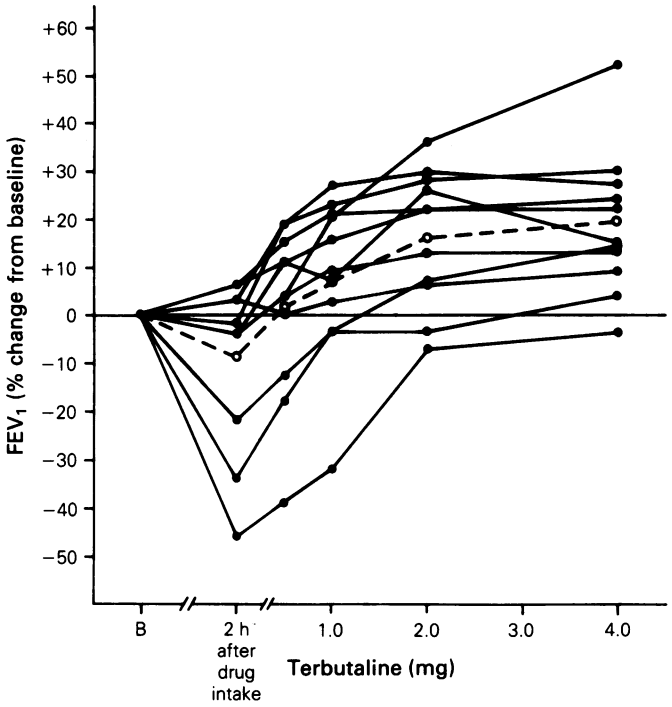

Figure 2 Individual changes of FEV_1, expressed as % change from baseline, 2 h after intake of xamoterol 200 mg and after subsequent inhalation of cumulative doses of terbutaline. O---O represents mean values.

patients with a lesser reversibility of their airways obstruction (Perks *et al.*, 1978). HR and systolic BP were significantly decreased by atenolol 50 mg, while there was a significant increase in these parameters after xamoterol 200 mg (Figure 1). Xamoterol therefore has at rest an inotropic effect, as shown by others previously (Rousseau *et al.*, 1983; Löfdahl & Svedmyr, 1984). The effects of xamoterol and atenolol on diastolic blood pressure were probably mediated by rest, since diastolic blood pressure also declined after placebo. Atenolol 50 mg induced a clear bronchoconstriction as can be concluded from the decrease in FVC and FEV_1 (Table 2 and Figure 1). In a previous study (Lammers *et al.*, 1985) we did not find an effect of atenolol 100 mg on FEV_1 in asthmatic patients at rest. After exercise, however, there was a significant fall in FEV_1 during atenolol 100 mg. The reaction of asthmatic patients to β_1-adrenoceptor selective antagonists, therefore, remains variable.

The increase in systolic BP by xamoterol is probably caused by the partial β_1-adrenoceptor agonist activity of this drug. Lung function, however, did not improve after intake of xamoterol, which might indicate an absence of β_1-adrenoceptor mediated bronchodilatation in man. The results of our study appear to correlate with radioligand binding studies *in vitro*, as Zaagsma *et al.* (1983) could not demonstrate β_1-adrenoceptors in human bronchial smooth muscle. Conversely, it seems that bronchoconstriction induced by β_1-adrenoceptor-selective blockers must be explained by a lack of selectivity of these drugs and not by a blockade of β_1-adrenoceptors in the bronchial smooth muscles. Studies with full β_1-adrenoceptor agonists and antagonists in asthmatic patients, however, are needed to solve these questions.

Xamoterol caused a bronchoconstriction in three patients, as can be concluded from the fall in their FEV_1 (Figure 2). Although these three patients had a reversibility of FEV_1 of more than 25%, other patients with a high reversibility did not show a decrease in lung function after xamoterol. Löfdahl & Svedmyr (1984) also described a fall of more than 20% in two out of eight asthmatic patients after an intravenous dose of xamoterol 0.1 mg kg^{-1}. As indicated above this bronchoconstrictor effect of xamoterol is presumably due to antagonism of β_2-adrenoceptors in the airways of these asthmatic patients.

The mean PEFR did not change significantly during either xamoterol or atenolol which was due mainly to intraindividual variations of this

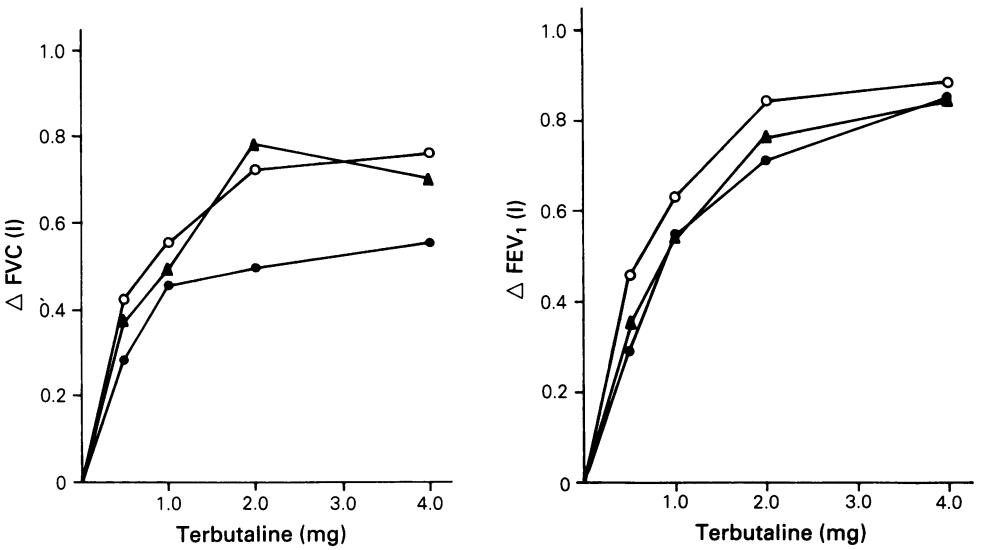

Figure 3 Mean changes in FVC and FEV_1 induced by terbutaline in cumulative doses as compared to values 2 h after intake of placebo (●), xamoterol 200 mg (▲) and atenolol 50 mg (○).

parameter. The variability found in this study, however, did not exceed the variability as described in the literature (Quanjer, 1983).

The improvement in lung function after inhalation of terbutaline was similar for atenolol, xamoterol and placebo (Table 2, Figure 3). Bronchospasm induced by atenolol 50 mg or xamoterol 200 mg, therefore, appears to be reversible with a β_2-adrenoceptor stimulant drug.

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References

American Thoracic Society (1962). Chronic bronchitis, asthma and pulmonary emphysema. A statement by the committee on diagnostic standards for non-tuberculous respiratory diseases. *Am. Rev. resp. Dis.*, **85**, 762–768.

Colton, Th.(1974). *Statistics in medicine.* Boston: Little, Brown and Co.

Connolly, C. K. (1979). Diurnal rhythms in airway obstruction. *Br. J. dis. Chest*, **73**, 357–366.

Cook, N., Richardson, A. & Barnett, D. B. (1984). Comparison of the β_1 selective affinity of prenalterol and corwin demonstrated by radioligand binding. *Eur. J. Pharmac.*, **98**, 407–412.

Ellis, M. E., Sahay, J. N., Chatterjee, S. S., Cruickshank, J. M. & Ellis, S. H. (1981). Cardioselectivity of atenolol in asthmatic patients. *Eur. J. Pharmac.*, **21**, 173–176.

Fleming, G. M., Chester, E. H., Schwartz, H. J. & Jones, P. K. (1978). Beta-adrenergic blockade of the lung. Dose-dependent cardioselectivity of tolamolol in asthma. *Chest*, **73**, 807–812.

Greefhorst, A. P. M. & Van Herwaarden, C. L. A. (1981). Comparative study of the ventilatory effects of three $beta_1$-selective blocking agents in asthmatic patients. *Eur. J. clin. Pharmac.*, **20**, 417–421.

Greefhorst, A. P. M. & Van Herwaarden C. L. A. (1983). Ventilatory and haemodynamic effects of prenalterol and terbutaline in asthmatic patients. *Eur. J. clin. Pharmac.*, **24**, 173–178.

Harry, J. D., Marlow, H. F., Wardleworth, A. G. & Young, J. (1981). The action of ICI 118587 (a β-adrenoceptor partial agonist) on the heart rate response to exercise in man. *Br. J. clin. Pharmac.*, **12**, 266P–267P.

Lammers, J. W. J., Folgering, H. Th. M. & Van Herwaarden, C. L. A. (1984). Ventilatory effects of $beta_1$-receptor-selective blockade with bisoprolol and metoprolol in asthmatic patients. *Eur. J. clin. Pharmac.*, **27**, 141–145.

Lammers, J-W. J., Folgering, H. Th. M. & Van Herwaarden, C. L. A. (1985). Ventilatory effects of bevantolol and atenolol in asthma. *Clin. Pharmac. Ther.*, **38**, 428–433.

Löfdahl, C-G. & Svedmyr, N. (1982). Effects of prenalterol in asthmatic patients. *Eur. J. clin. Pharmac.*, **23**, 297–302.

Löfdahl, C-G. & Svedmyr, N. (1984). Effects of xamoterol (ICI 118,587) in asthmatic patients. *Br.*

J. clin. Pharmac., **18**, 597–601.

McNeill, R. S. (1964). Effect of a beta-adrenergic-blocking agent, propranolol, on asthmatics. *Lancet*, **ii**, 1101–1102.

Melander, A., Danielson, K., Schersten, B. & Wählin, E. (1977). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmac. Ther.*, **22**, 108–112.

Newman, S. P., Morén, F., Pavia, D., Little, F. & Clarke, S. W. (1981). Deposition of pressurized suspension aerosols inhaled through extension devices. *Am. Rev. resp. Dis.*, **124**, 317–320.

Nuttall, A. & Snow, H. M. (1982). The cardiovascular effects of ICI 118, 587: a β_1-adrenoceptor partial agonist. *Br. J. Pharmac.*, **77**, 381–388.

O'Neill, P. A., Morton, P. B., Sharman, P., Marlow, H. F. & Stark, R. D. (1984). The effects of ICI 118,587 and atenolol on the response to exercise and on breathlessness in healthy subjects. *Br. J. clin. Pharmac.*, **17**, 37–41.

Perks, W., Chatterjee, S. S., Croxson, R. S. & Cruickshank, J. M. (1978). Comparison of atenolol and oxprenolol in patients with angina or hypertension and co-existent chronic airways obstruction. *Br. J. clin. Pharmac.*, **5**, 101–106.

Quanjer, Ph. H. (Ed.) (1983). Standardized lung function testing. *Clin. resp. Physiol.*, **19**, Suppl. 5, 1–95.

Rousseau, M. F., Pouleur, H. & Vincent, M-F. (1983). Effects of a cardioselective $beta_1$ partial agonist (Corwin) on left ventricular function and myocardial metabolism in patients with previous myocardial infarction. *Am. J. Cardiol.*, **51**, 1267–1274.

Rugg, E. L., Barnett, D. B. & Nahorski, S. R. (1978). Coexistence of $beta_1$ and $beta_2$ adrenoceptors in mammalian lung: evidence from direct binding studies. *Mol. Pharmac.*, **14**, 996–1005.

Zaagsma, J., Van der Heijden, P. J. C. M., Van der Schaar, M. W. G. & Bank, C. M. C. (1983). Comparison of functional beta-adrenoceptor heterogeneity in central and peripheral airway smooth muscle of guinea pig and man. *J. receptor Res.*, **4**, 89–106.

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