British Heart Journal, 1978, **40**, 184-189

Beta-blockers and asthma

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SUMMARY In a single-blind, randomised, crossover study in 10 asthmatic patients, the effects of approximately equipotent oral doses of 3 cardioselective beta-blockers—atenolol (100 mg), metoprolol (100 mg), and acebutolol (300 mg)—and 4 non-cardioselective beta-blockers—propranolol (100 mg), oxprenolol (100 mg), pindolol (5 mg), and timolol (10 mg) upon FEV_1 were compared.

All drugs, except pindolol, produced a significant reduction in standing pulse rate and prevented any increase in heart rate after inhaled isoprenaline (1500 μg). All drugs caused a fall in FEV_1 but only atenolol did not differ significantly from placebo in this respect. The bronchodilator response to inhaled isoprenaline was blocked by the 4 non-cardioselective drugs; the 3 cardioselective agents permitted some bronchodilatation, but only atenolol did not differ from placebo.

Hypertension, ischaemic heart disease, cardiac arrhythmias, and asthma are common conditions often occurring, in various combinations, in the same patient. Beta-adrenoreceptor antagonists (beta-blockers) are frequently administered for the first three ailments but are known to be potentially harmful to the asthmatic. Since the demise of practolol in 1975, there has been a need for a beta-blocker which might be given with relative safety to the asthmatic patient.

The present study was designed to assess the effect of 7 established beta-blockers upon the airways resistance of a group of patients with reversible airways obstruction. The 7 agents were: 2 non-cardioselective beta-blockers with no intrinsic sympathomimetic activity—propranolol (Inderal), and timolol (Blocadren); 2 non-cardioselective beta-blockers with intrinsic sympathomimetic activity—pindolol (Visken) and oxprenolol (Trasicor); 2 cardioselective beta-blockers with no intrinsic sympathomimetic activity—metoprolol (Lopressor or Betaloc) and atenolol (Tenormin); and 1 cardioselective agent with intrinsic sympathomimetic activity—acebutolol (Sectral).

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Received for publication 26 September 1977.

Methods

Ten asthmatic patients were included in the study, all with reversible airways obstruction. Clinical features are listed in Table 1.

Five of the patients were seen at Wythenshawe Hospital, Manchester, and had previously been exposed (single-blind randomised, crossover) to single oral doses of propranolol (100 mg), metoprolol (100 mg), atenolol (100 mg), and placebo. All 5 patients had had a fall in FEV_1 of at least 20 per cent to one or more of those beta-blockers. The study was extended so that 4 of the 5 patients received single oral doses (single-blind, randomised, crossover) of timolol (10 mg) and oxprenolol (100 mg).

The other 5 patients were seen at the Cardiothoracic Centre, Southampton, and had been previously exposed (under identical conditions to the Manchester study) to propranolol (100 mg), pindolol (5 mg), acebutolol (300 mg), atenolol (100 mg), and placebo. As before, all 5 patients had had a fall in FEV_1 of at least 20 per cent to one or more of those beta-blockers. The study was extended so that 4 of the 5 patients received single oral doses (single-blind, randomised, crossover) of metoprolol (100 mg) and oxprenolol (100 mg). Drug dosage was chosen according to accepted beta-blocking potency ratios in man (Thadani *et al.*

Table 1 *Clinical features*

Hospital	*Subject*	*Sex*	*Age*	*Atopic status (extrinsic = +) (intrinsic = −)*	*Treatment*
Wythenshawe (Manchester)	1	M	62	−	Franol*
	2	M	59	+	Salbutamol Sodium cromoglycate
	3	M	45	+	Salbutamol Beclomethasone dipropionate
	4	F	54	−	Salbutamol Sodium cromoglycate Debrisoquine (hypertension)
	5	M	51	−	Salbutamol Debrisoquine (hypertension) Methyldopa (hypertension)
Cardiothoracic Centre (Southampton)	6	M	22	+	Salbutamol Beclomethasone dipropionate
	7	M	19	+	Salbutamol Beclomethasone dipropionate
	8	M	17	+	Salbutamol Sodium cromoglycate Beclomethasone dipropionate
	9	M	19	+	Salbutamol
	10	M	65	−	Salbutamol

*Epidrine hydrochloride + theophylline + phenobarbitone.

1973; Taylor *et al.*, 1974; Bühler *et al.*, 1975; Conway *et al.*, 1976; Davidson *et al.*, 1976) and also was considered to be close to dose levels used in clinical practice. The study had been approved by the two Hospital Ethical Committees and full patient consent obtained.

PROCEDURE

This was identical for the 2 hospitals. The patients attended on 7 occasions (Southampton) and 6 occasions (Manchester), and all studies were performed at the same time of day. Each visit was separated by at least 2 days. They were asked to avoid taking bronchodilators for 12 hours beforehand but to remain on disodium cromoglycate or steroids if they were part of their usual treatment. Measurements were made of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) using a Vitalograph spirometer, and of peak expiratory flow rate (PEFR) using a Wright's peak flow meter. In addition, standing heart rate was recorded. The standing pulse rate is influenced more by sympathetic and less by vagal discharge than is the supine pulse rate (Kofi Ekue *et al.*, 1974), and was, therefore, used in this study. Though suppression of the tachycardia associated with severe exercise (where there is little or no vagal influence) is the ideal way of assessing beta-blockade, some investigators have found that standing produces an assessment of beta-blockade not dissimilar from that obtained by more elaborate methods, i.e. severe exercise (Carruthers *et al.*, 1974; Kofi Ekue *et al.*, 1974). Moreover, such a simple method is easy to use in outpatient clinics—as in the present study.

The schedule at each visit was as follows: 9.00 am and 9.30 am baseline measurements were made. A single oral dose of one of the drugs was then given and measurements were repeated at 10.30 am and 11.30 am. 1500 μg isoprenaline sulphate was given by aerosol and measurements were repeated at 5-minute intervals for the next 15 minutes. Measurements were not extended beyond 2 hours after drug administration as peak blood levels and maximal beta-blockade occur at about this time.

STATISTICAL METHOD

An analysis of covariance was used to establish if and to what extent the baseline influenced the 2-hour and isoprenaline results. Adjusted means were obtained from this analysis and were compared using a t test with the residual mean square as the estimate of variance. A paired t test was used to perform the within-drug comparison. (The sequence for the original data sets and for the 2 extra drugs was checked by performing an analysis of variance. To analyse the combined data set, an analysis of covariance was performed using the baseline for each treatment as the covariate. This was done twice, once with the group × drug interaction included, and once, after we had found non-significance, without.)

To check that the additional drugs (in the 2 extended studies) produced no sequential effect when added to the drugs in the 2 main studies, the metoprolol/placebo comparison (one in a main, and

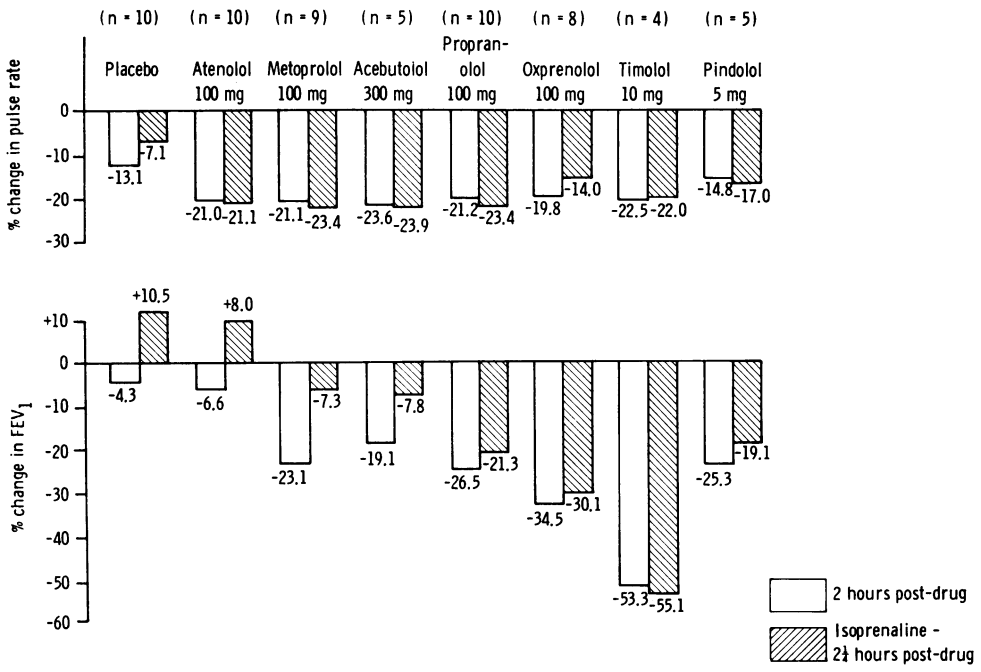

Fig. *Effect of drugs (percentage change from baseline) and isoprenaline upon standing pulse rate (beats/min) and FEV_1 (litres).*

the other in an extended study) was examined. No significant difference was found.

Results

All drugs, with the exception of pindolol, were associated with an almost identical percentage decrease in standing heart rate (Fig.), thus confirming equipotency of beta-blockade. These results, again with the exception of pindolol, were statistically significantly ($P < 0.05$) slower than that associated with placebo. Isoprenaline caused a speeding of the pulse rate while patients were taking placebo, though this did not achieve statistical significance.

The effects of drugs upon FVC, PEFR, and FEV_1 were almost identical. For simplicity, results referring only to FEV_1 will be presented. Table 2 shows the effect of the drugs and isoprenaline upon the FEV_1 of the 10 patients. At some time during the study, 6 of the 10 patients complained of wheezing induced by one or more of the drugs. This was so for all 4 patients who received timolol; 6 of the 8 patients who received oxprenolol; 5 of the 10 patients who received propranolol; 4 of the 9 patients who received metoprolol; and 1 of the 5 patients who received both pindolol and acebutolol. No wheezing was associated with either placebo or atenolol.

All drugs caused a fall in the mean FEV_1 at 2 hours (Table 3, Fig.). The fall in FEV_1 associated with atenolol, in contrast to all the other drugs, did not differ statistically significantly from placebo (Table 4). The falls in FEV_1 associated with oxprenolol, pindolol, propranolol, and timolol were all statistically significantly greater than that seen with atenolol (Table 4).

The effects of isoprenaline (given 2¼ hours after drug administration) upon FEV_1 are shown in Table 3 and the Fig. Only in the case of placebo and the 3 cardioselective drugs, atenolol, metoprolol, and acebutolol, was a bronchodilator action observed, achieving statistical significance in the case of placebo ($P < 0.001$), atenolol ($P < 0.01$), and metoprolol ($P < 0.05$).

The FEV_1 achieved after isoprenaline exceeded baseline values only in the cases of placebo and atenolol (Table 3, Fig.). In a 'between-drug' comparison of the difference between initial and post-isoprenaline FEV_1 values (Table 4), the FEV_1 was statistically significantly higher on placebo than on all drugs except atenolol. Similarly, the post-isoprenaline FEV_1 values were significantly higher

2 *Effect of treatment upon FEV_1 (litres)*

l	Pat. No.	Placebo n = 10			Atenolol n = 10			Propranolol n = 10			Metoprolol n = 9			Oxprenolol n = 8			Timolol n = 4			Acebutolol n = 5			Pindolol n = 5		
		B	*2*	*Iso*	*B*	*2*	*Iso*	*B*	*2*	*Iso*	*B*	*2*	*Iso*	*B*	*2*	*Iso*	*B*	*2*	*Iso*	*B*	*2*	*Iso*	*B*	*2*	*Iso*
ıshawe	1	0·75	0·70	0·90	0·75	0·60	0·70	*0·70*	*0·50*	*0·60*	0·75	0·60	0·70	*0·55*	*0·45*	*0·40*	*0·53*	*0·40*	*0·40*	—	—	—	—	—	—
.chester)	2	1·65	1·45	2·10	1·65	1·35	1·80	*1·95*	*1·00*	*1·20*	*1·75*	*1·10*	*1·70*	*1·10*	*0·65*	*0·60*	*1·25*	*0·70*	*0·60*	—	—	—	—	—	—
	3	3·85	3·60	4·00	2·90	2·65	3·70	3·55	3·15	3·60	3·60	3·20	3·60	—	—	—	—	—	—	—	—	—	—	—	—
	4	2·25	2·25	2·30	2·15	1·80	2·00	*1·95*	*1·40*	*1·70*	*2·20*	*1·70*	*1·70*	*2·10*	*1·35*	*1·50*	*2·05*	*1·25*	*1·30*	—	—	—	—	—	—
	5	2·00	1·30	1·60	0·90	0·95	1·00	1·60	1·10	1·30	2·20	1·00	1·30	*1·00*	*0·65*	*0·80*	*2·85*	*0·75*	*0·70*	—	—	—	—	—	—
horacic Centre	6	3·28	3·00	3·50	3·60	3·23	3·20	*3·28*	*2·50*	*2·60*	*2·63*	*1·45*	*1·65*	*2·84*	*1·93*	*2·09*	—	—	—	2·83	2·50	2·75	3·35	3·25	3·35
thampton)	7	4·20	3·88	4·55	3·45	3·40	3·85	*3·60*	*2·80*	*3·10*	*3·40*	*2·33*	*3·60*	*3·75*	*1·20*	*1·55*	—	—	—	*3·30*	*1·58*	*2·40*	*3·98*	*1·73*	*2·50*
	8	2·38	2·78	2·95	1·48	1·45	2·20	2·03	1·28	0·85	—	—	—	—	—	—	—	—	—	1·90	2·05	1·85	1·70	1·15	1·10
	9	4·05	4·10	4·75	4·38	3·98	4·40	4·50	3·55	3·60	3·75	3·95	4·45	3·83	3·40	3·40	—	—	—	4·45	3·95	4·20	4·95	4·05	3·85
	10	1·23	1·43	1·95	1·80	1·73	2·25	1·75	1·00	1·05	1·95	1·75	1·95	1·33	1·15	1·15	—	—	—	1·65	1·35	1·85	1·43	1·30	1·75

aseline; 2 = 2 hours after treatment; Iso = Isoprenaline given 2½ hours after treatment; n = number of patients.
given in italics indicate that the patient complained of wheeziness.

Table 3 *Mean standing pulse rates (beats/min) and FEV_1 (litres) at baseline (B), 2 hours after treatment (2), and after isoprenaline given 2½ hours after treatment (Iso)*

No.	*Treatment*		*Pulse rate*			*FEV_1*		
			B	*2*	*Iso*	*B*	*2*	*Iso*
10	Atenolol		84·9	67·3	67·0	2·31	2·11	2·51
		SE	(5·58)	(4·58)	(4·36)	(0·39)	(0·36)	(0·39)
10	Propranolol		83·5	65·8	63·9	2·49	1·83	1·96
		SE	(5·39)	(3·79)	(3·33)	(0·37)	(0·34)	(0·37)
8	Oxprenolol		79·7	64·0	68·7	2·06	1·35	1·44
		SE	(4·63)	(2·31)	(3·38)	(0·45)	(0·34)	(0·34)
9	Metoprolol		82·7	65·3	65·5	2·47	1·90	2·29
		SE	(5·04)	(3·62)	(4·36)	(0·33)	(0·36)	(0·42)
4	Timolol		85·0	65·7	66·2	1·67	0·78	0·75
		SE	(5·87)	(2·66)	(4·09)	(0·50)	(0·18)	(0·19)
5	Acebutolol		83·0	63·4	62·8	2·83	2·29	2·61
		SE	(6·12)	(3·23)	(2·06)	(0·51)	(0·46)	(0·43)
5	Pindolol		78·6	67·0	65·2	3·08	2·30	2·51
		SE	(4·95)	(3·35)	(4·32)	(0·67)	(0·58)	(0·50)
10	Placebo		83·8	73·7	78·2	2·56	2·45	2·86
		SE	(5·31)	(3·88)	(4·65)	(0·39)	(0·38)	(0·41)

SE = Standard error of mean

on atenolol than on oxprenolol, pindolol, propranolol, and timolol; and significantly higher on metoprolol than on oxprenolol and timolol.

Discussion

The results of this study complement those of Harms (1977) who compared the effects of 6 beta-blockers (propranolol, pindolol, practolol, atenolol, metoprolol, and acebutolol) *in vitro* (animal and human tissue) and *in vivo* (dog). He derived a cardioselectivity index (pA_2 against isoprenaline on atrial beta-1 receptors minus pA_2 against isoprenaline on bronchial beta-2 receptors) for the 6 agents. The *in vitro* indices (mean of 4 separate studies) were: atenolol, 1·63; practolol, 1·73; acebutolol, 1·50; metoprolol, 1·23; propranolol, 0·23; and pindolol, 0·08. The *in vivo* indices were similar: atenolol, 1·78; practolol, 1·67; metoprolol, 1·68; acebutolol, 1·67; pindolol, 0·56; and propranolol, 0·41. These laboratory data appear to be good predictors of how the various beta-blockers will behave when given to the asthmatic patient; particularly in relation to their modifying effect upon the bronchodilator action of isoprenaline, i.e. cardioselective, in contrast to non-cardioselective, agents permit a significant bronchodilatation. The study by Vilsvik and Schaanning (1976), comparing

Table 4 *Between-treatment comparisons of effects upon FEV_1—statistical significance.*

Parameter	*Treatments*	*Significance*
Difference between initial and 2 hours after treatment FEV_1 values	Plac v Aceb	*
	Plac v Met	†
	Plac v Ox	‡
	Plac v Pind	†
	Plac v Prop	†
	Plac v Tim	†
	Aten v Ox	†
	Aten v Pind	*
	Aten v Prop	*
	Aten v Tim	*
Difference between initial and after isoprenaline (given 2½ hours after treatment) FEV_1 values	Plac v Aceb	†
	Plac v Met	†
	Plac v Ox	‡
	Plac v Pind	‡
	Plac v Prop	‡
	Plac v Tim	‡
	Aten v Ox	‡
	Aten v Pind	*
	Aten v Prop	†
	Aten v Tim	‡
	Aceb v Ox	*
	Met v Ox	†
	Met v Tim	*

Key: Plac = Placebo, Aten = Atenolol, Met = Metoprolol, Aceb = Acebutolol, Prop = Propranolol, Ox = Oxprenolol, Tim = Timolol, Pind = Pindolol

* = $P < 0.05$

† = $P < 0.01$

‡ = $P < 0.001$

the effects of atenolol and practolol in 12 asthmatic patients, confirmed these points when they showed that atenolol was slightly more cardioselective than practolol in man.

Two points should be stressed on dosage. Firstly, in the present study, single oral doses were used, and the results cannot necessarily be applied to chronic dosing. However, Henningsen (1977) reported that of 17 hypertensive asthmatic patients taking atenolol, 16 were well on the drug after 3 years. Secondly, cardioselectivity is a dose-related quality (Lertora *et al.*, 1975; Singh *et al.*, 1975). This point has been well shown in man (Formgren, 1976) where bronchospasm was induced by metoprolol at doses above 100 mg/day.

It was noteworthy that all the drugs blocked the beta-1 effect of isoprenaline upon the pulse rate. The non-cardioselective drugs also blocked the beta-2 effect of isoprenaline upon the bronchi, in contrast to the drugs claiming cardioselectivity which permitted some bronchodilator activity. Again, this point was emphasised by Vilsvik in his atenolol/practolol comparison.

In conclusion, no beta-blocker, even if claiming to be cardioselective, is absolutely safe for the asthmatic patient. Neither does the possession of intrinsic sympathomimetic activity appear to have a beneficial effect, as claimed by some investigators (Macdonald and McNeill, 1968; Paterson, 1971; Imhof, 1974). However, the bronchodilator action of a beta-2 stimulant such as isoprenaline is best preserved by giving a cardioselective, rather than non-cardioselective, beta-blocker.

We thank Dr. T. G. Radha for her help, and Nigel Barker for his statistical assistance.

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