COMPARISON OF ATENOLOL AND OXPRENOLOL IN PATIENTS WITH ANGINA OR HYPERTENSION AND CO-EXISTENT CHRONIC AIRWAYS OBSTRUCTION

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- 1 The effects of atenolol (50 mg and 100 mg) and oxprenolol (80 mg) on respiratory function were studied in ten patients with angina pectoris or hypertension complicated by chronic airways obstruction.
- 2 In patients with 'fixed' airways obstruction, neither atenolol nor oxprenolol significantly affected airways resistance.
- 3 In patients with 'labile' airways obstruction, atenolol did not produce a significant increase in airways obstruction, whereas oxprenolol did.
- 4 Following isoprenaline challenge (1500 μ g by inhalation), atenolol permitted full bronchodilatation, whereas oxprenolol almost completely blocked the action of isoprenaline.
- 5 Partial agonist activity appears to be of less clinical importance than cardioselectivity.

Introduction

Atenolol ('Tenormin'*, ICI 66,082) is a new β -adrenoceptor antagonist which is equipotent with propranolol in suppressing exercise-tachycardia (Conway, Fitzgerald, McAinsh, Rowlands & Simpson, 1976). Animal experiments have demonstrated cardioselectivity, an absence of both partial agonist activity (intrinsic sympathomimetic activity) and membrane stabilizing activity (MSA), and that atenolol does not cross the blood-brain barrier. In contrast to propranolol, intravenous use in man of atenolol has been shown to cause minimal changes in airways conductance (Astrom & Vallin, 1974). The use of non-cardioselective β -adrenoceptor antagonists has in the past been contraindicated in asthmatic patients. However, it has been claimed that non-cardioselective β -adrenoceptor antagonists possessing intrinsic sympathomimetic activity (ISA) are relatively safe when administration to asthmatics (Connolly & Batten, 1970; Paterson, 1971).

The present study in patients with chronic airways obstruction with either angina or hypertension was designed (a) to compare the effects upon airways obstruction of oral atenolol and oxprenolol, a non-cardioselective β -adrenoceptor antagonist possessing ISA, and (b) to observe the bronchodilator effect of an isoprenaline inhalant administered subsequently.

Methods

Ten patients, eight men and two women, were studied in this trial. All had either angina pectoris or

hypertension complicated by chronic airways obstruction. Patients were excluded if they had a history of cardiac failure, or second or third degree heart block.

Patient details are given in Table 1. The mean age of the men was 56.5 years (range 43–63) and the women 54 years (range 52–56).

The study was designed as a double-blind cross-over comparison in which each patient received each of the following in identical form: atenolol 50 mg, atenolol 100 mg, oxprenolol 80 mg and placebo. Patients then received an isoprenaline challenge of 1500 μ g consisting of three puffs, 30 s apart, of 'Medihaler ISO Forte'.

Respiratory function (RF) was assessed by forced expiratory volume in 1 s (FEV₁) measured by dry wedge spirometer, and by airways resistance (AWR) measured by whole body plethysmography.

All patients were fully acquainted with the above methods and apparatus before entering the trial.

The study had been approved by the Hospital Ethical Committee. Details of procedure were explained to the patients and their full consent was obtained. They were then randomly allocated to the first treatment group: the other three treatments were randomly administered at weekly intervals. Before each treatment, bronchodilator drugs were withheld for 12 h, but patients on disodium cromoglycate or steroids were asked to remain on them. The schedule at each visit to the clinic was the same and as follows:

09 h 00 min— Reports after light breakfast

- 09 h 15 min— Respiratory function tests (RFTs) and heart rate (HR)
 09 h 30 min— Repeat RFT and HR, then given single oral dose
 10 h 30 min— Repeat RFTs and HR
 11 h 30 min— Repeat RFTs and HR
 11 h 45 min— Administer 1500 µg isoprenaline sulphate
 12 h 00 min— RFTs and HR

Pre-isoprenaline observations were not extended beyond two hours as optimal blood levels of both drugs are achieved by 2 h (Reiss, Rajagopalan, Imhof, Schmid & Keberle, 1970; Conway *et al.*, 1976).

Results were analysed using the Student's *t*-test for paired data.

Results

Heart rate

Table 2 illustrates heart rate associated with placebo and the three active treatments. All three produced a statistically significant reduction as compared to placebo, but their effects did not differ significantly.

Respiratory function tests

In the ten patients, two groups are recognizable

1. Four (patients 1, 3, 9 and 10) whose airway resistance showed little change either with the three active treatments or after isoprenaline (less than 15% change from basal value): these patients thus have 'fixed' airways obstruction, and
2. Six whose airway resistance did change when active treatments and isoprenaline were administered: these patients appear to have 'labile' airways obstruction.

'Fixed' airways obstruction. Figure 1 illustrates that (a) the active treatments do not adversely affect FEV₁ or AWR, and (b) the bronchodilator effect of isoprenaline is absent in the case of oxprenolol and modest (less than 15% change from basal value) for both doses of atenolol. No within- or between-treatment comparisons achieve statistical significance.

'Labile' airways obstruction. Figure 2 shows that it is the 'labile' patient who differentiates between a cardioselective and non-cardioselective β -adreno-

Table 1 Individual patient data

Number	Sex	Age (years)	Weight (kg)	Past medical history	Treatment
1	M	59	64	(1) Angina (2) Intrinsic asthma	Previously on practolol Salbutamol
2	M	63	72	(1) Angina (2) Extrinsic asthma	Perhexiline – 1 two times daily Verapamil – 1 three times daily Trinitrin
3	M	63	72	(1) Angina (2) Intrinsic asthma	Trinitrin
4	M	55	80	(1) Angina (2) Intrinsic asthma	Salbutamol Prednisolone – 3 mg/day Ephedrine – three times a day Trinitrin
5	F	52	67	(1) Hypertension (2) Extrinsic asthma	Salbutamol Debrisoquine
6	F	56	49	(1) Angina (2) Extrinsic asthma	Beclomethasone Salbutamol Oxprenolol (did not exacerbate asthma)
7	M	58	64	(1) Hypertension (2) Intrinsic asthma	Bendrofluazide Potassium chloride Propranolol (did exacerbate asthma)
8	M	43	67	(1) Angina (mild) (2) Extrinsic asthma	Beclomethasone Trinitrin
9	M	56	68	(1) Hypertension (2) Angina (3) Intrinsic asthma	Methyldopa Bendrofluazide Salbutamol Trinitrin
10	M	55	61	(1) Angina (2) Extrinsic asthma	Oxprenolol (did not exacerbate asthma) Beclomethasone Salbutamol Practolol reported to have made him worse

Figure 1 Effect of four treatments and isoprenaline (ISO) on FEV_1 and airways resistance (AWR) in fixed airways group (four patients). ● oxprenolol (80 mg); ○ atenolol (50 mg); △ atenolol 100 mg; ▲ placebo.

ceptor antagonist, particularly in the degree of bronchodilator response to isoprenaline.

Forced expiratory volume (FEV_1).

Within-treatment comparisons are shown in Tables 3 and 4. With oxprenolol there is a statistically significant depression of FEV_1 at both 1 and 2. There

Table 2 Pulse rate (beats/min) mean values ($\pm$ s.e. mean) before the four treatments (B), 1 and 2 h post-treatment (1 and 2), and post-isoprenaline (ISO)

	Oxprenolol (80 mg)	Atenolol (50 mg)	Atenolol (100 mg)	Placebo
B	77.4 $\pm$ 4.43	77.4 $\pm$ 3.68	82.2 $\pm$ 4.95	82.4 $\pm$ 4.36
1	64.3 $\pm$ 2.72	65.3 $\pm$ 4.15	62.8 $\pm$ 3.08	76.3 $\pm$ 3.86
2	63.4 $\pm$ 3.11	58.8 $\pm$ 3.10	59.6 $\pm$ 2.78	70.9 $\pm$ 3.88
ISO	61.5 $\pm$ 2.91	63.0 $\pm$ 2.18	60.5 $\pm$ 3.04	79.8 $\pm$ 3.73

Figure 2 Effect of four treatments and isoprenaline (ISO) on FEV_1 and airways resistance (AWR) in labile airways group (six patients). ○ oxprenolol (80 mg); ○ atenolol (50 mg); △ atenolol (100 mg); ▲ placebo.

is a non-significant bronchodilator effect of isoprenaline, resulting in an FEV_1 lower than the base-line value. In contrast, both doses of atenolol cause a non-significant depression of FEV_1 at 1 and 2 h, but permit (as did placebo) a significant bronchodilator effect of isoprenaline resulting in a final FEV_1 substantially exceeding the base-line value.

Between-treatment comparisons are shown in Table 5. It can be seen that (a) oxprenolol causes a significantly greater depression of FEV_1 at 1 and 2 h than placebo and both doses of atenolol, (b) the bronchodilator effect of isoprenaline is significantly greater after placebo and both doses of atenolol than after oxprenolol, (c) there is no difference between both doses of atenolol, and (d) both doses of atenolol cause significantly greater depression of FEV_1 at 2 h than placebo.

Airways resistance

Figure 2 and Table 6 reveal similar changes in AWR associated with the four treatments as are described in the above section on FEV_1 .

In spite of changes in objective measurements in respiratory function, no patient complained of side effects or a change in respiratory symptoms during any of the treatments.

Discussion

FEV₁ and AWR are measures of airways function. FEV₁ is measured during forced expiration and reflects changes in both small and large airways. AWR is measured during quiet breathing and reflects mainly changes in large airways. Both methods are complementary, and in this study reveal almost identical trends.

The cardioselective nature of atenolol was confirmed by the blocking of the increase in pulse-rate with isoprenaline (β_1 -receptor activity), while permitting the associated bronchodilator effect

(β_2 -receptor activity). Oxprenolol was non-cardio-selective in that it blocked both the increase in pulse-rate and bronchodilator action associated with isoprenaline.

Atenolol, though causing a significantly lesser increase in bronchial obstruction than oxprenolol, nevertheless does induce some increase. In this respect, in common with other β -adrenoceptor antagonists claiming cardioselective activity [practolol (Bernecker & Roetscher, 1970; Waal-Manning & Simpson, 1971; Formgren, 1972), acebutolol (Skinner & Palmer, 1974) and metoprolol (Johnsson, Svedmyr & Thiringer, 1975)], atenolol does pose a potential

Table 3 Labile patients: Within-treatment comparison of mean $\pm$ s.e. mean values of FEV₁ (l) before the four treatments and 1 and 2 h post-treatment

Oxprenolol (80 mg)			Atenolol (50 mg)			Atenolol (100 mg)			Placebo		
Before	1 h	P value	Before	1 h	P value	Before	1 h	P value	Before	1 h	P value
1.746 $\pm$ 0.169	1.508 $\pm$ 0.167	<0.01	1.883 $\pm$ 0.229	1.875 $\pm$ 0.186	NS	1.912 $\pm$ 0.226	1.883 $\pm$ 0.209	NS	2.013 $\pm$ 0.211	2.050 $\pm$ 0.210	NS
Before	2 h	P value	Before	2 h	P value	Before	2 h	P value	Before	2 h	P value
1.746 $\pm$ 0.169	1.533 $\pm$ 0.126	<0.05	1.883 $\pm$ 0.229	1.750 $\pm$ 0.218	NS	1.912 $\pm$ 0.226	1.717 $\pm$ 0.205	NS	2.013 $\pm$ 0.211	2.050 $\pm$ 0.137	NS

Table 4 Labile patients: Within-treatment comparison of mean $\pm$ s.e. mean values of FEV₁ (l) 2 h post-treatment and post-isoprenaline (ISO)

Oxprenolol (80 mg)			Atenolol (50 mg)			Atenolol (100 mg)			Placebo		
2 h	ISO	P value	2 h	ISO	P value	2 h	ISO	P value	2 h	ISO	P value
1.533 $\pm$ 0.126	1.658 $\pm$ 0.159	NS	1.750 $\pm$ 0.218	2.183 $\pm$ 0.171	<0.01	1.717 $\pm$ 0.205	2.167 $\pm$ 0.207	<0.01	2.050 $\pm$ 0.137	2.300 $\pm$ 0.260	<0.05

Table 5 Labile patients: Between treatment comparison of mean values of FEV₁ before the four treatments (B), 1 and 2 h post-treatment and post-isoprenaline (ISO), showing only P values

	Oxprenolol (80 mg)	Oxprenolol (80 mg)	Oxprenolol (80 mg)	Atenolol (50 mg)	Atenolol (50 mg)	Atenolol (100 mg)
	v	v	v	v	v	v
	Atenolol (50 mg)	Atenolol (100 mg)	Placebo	Atenolol (100 mg)	Placebo	Placebo
	P value	P value	P value	P value	P value	P value
B	NS	NS	<0.05	NS	NS	NS
1	<0.01	<0.01	<0.01	NS	NS	NS
2	<0.05	<0.01	<0.01	NS	<0.05	<0.05
ISO	<0.001	<0.01	<0.01	NS	NS	<0.05

Table 6 Labile patients: Within-treatment comparison of mean $\pm$ s.e. mean values of airways resistance ($\text{cm H}_2\text{O l}^{-1} \text{s}^{-1}$) before the four treatments, 2 h post-treatment and post-isoprenaline (ISO)

Oxprenolol (80 mg)			Atenolol (50 mg)			Atenolol (100 mg)			Placebo		
Before	2 h	P value	Before	2 h	P value	Before	2 h	P value	Before	2 h	P value
5.53 $\pm$ 0.89	7.44 $\pm$ 0.97	<0.05	5.63 $\pm$ 1.66	5.74 $\pm$ 1.26	NS	4.55 $\pm$ 1.33	6.77 $\pm$ 1.24	NS	3.64 $\pm$ 1.26	4.03 $\pm$ 0.90	NS
2 h	ISO	P value	2 h	ISO	P value	2 h	ISO	P value	2 h	ISO	P value
7.44 $\pm$ 0.37	6.55 $\pm$ 0.66	NS	5.74 $\pm$ 1.26	2.47 $\pm$ 0.37	<0.05	6.77 $\pm$ 1.24	2.23 $\pm$ 1.16	NS	4.03 $\pm$ 0.09	2.11 $\pm$ 1.47	NS

hazard to asthmatics. Skinner & Palmer (1974) conclude that any β -adrenoceptor blocking drug must be used with extreme caution in asthmatics, and Johnsson *et al.* (1975) go as far as to recommend that the cardioselective β -adrenoceptor antagonist metoprolol should be given to asthmatics only if it is combined with a β_2 -receptor-stimulating drug.

The most obvious difference between oxprenolol and atenolol is shown in the degree of bronchodilator response to isoprenaline observed 2.5 h after administration of the β -adrenoceptor-blocking drug. This response is almost complete after both doses of atenolol, and is similar to that after placebo. In contrast, oxprenolol produced marked inhibition of the bronchodilator response, and prevented ventilatory function returning to basal values. Thus, for optimal conditions for testing β -adrenoceptor antagonists it is important that the bronchi are subjected to an increase in sympathetic stimulation. Kumana, Kaye, Leighton, Turner & Hamer (1975) used vigorous exercise to achieve this, and under these conditions showed no difference between propranolol and acebutolol. Johnsson *et al.* (1975) used isoprenaline infusion and demonstrated that metoprolol permitted an excellent bronchodilator response in contrast to propranolol which almost completely blocked this effect. Similarly Skinner & Palmer (1974), using isoprenaline aerosol, demonstrated that practolol was cardioselective and acebutolol relatively less selective.

Not all patients with airways obstruction react in

the same way when given a β -adrenoceptor antagonist. In this study, the four 'fixed' asthmatics appeared resistant to the effects of both isoprenaline and β -adrenoceptor antagonists. The idea of 'fixed' and 'labile' airways obstruction is not a new one. Nordstrom, MacDonald & Gobel (1975) have recently highlighted this concept, and emphasized that propranolol could be given to the 'fixed' variety with relative safety. Such patients also showed little reversibility of airways obstruction when bronchodilator agents were given: indeed there appeared to be a reasonable correlation between reversibility of airways obstruction following isoprenaline inhalation and the decrease in FEV_1 during administration of propranolol.

There might be some justification for concluding that if a patient with chronic airways obstruction has an increase in FEV_1 of less than 15% of the basal value when isoprenaline inhalant is administered, then β -adrenoceptor antagonists, both cardioselective and non-cardioselective, can be given with reasonable safety. However, if the patient falls into the 'labile' category, only a genuine cardioselective β -adrenoceptor antagonist should be used, possibly with the addition of a bronchodilator agent.

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