ASSESSMENT OF β -ADRENOCEPTOR ANTAGONISTS IN ASTHMATIC PATIENTS

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1 Bronchial smooth muscle, skeletal muscle and cardiac β -adrenoceptor antagonism have been compared in twelve asthmatic patients after three β -adrenoceptor antagonists at two dose levels. The non-selective antagonist propranolol (40 and 160 mg), the non-selective antagonist with partial agonist activity pindolol (5 and 20 mg) and the β_1 -selective antagonist atenolol (50 and 200 mg) were studied on separate occasions.

2 Six placebo days were used in this double-blind crossover study to allow interpretation of individual as well as group results.

3 Bronchial smooth muscle effects were assessed by resting spirometry, histamine inhalation test and spirometric response to inhaled fenoterol. Skeletal muscle effects were assessed by resting tremor and fenoterol induced tremor.

4 Cardiac β -adrenoceptor antagonism was assessed by measuring the effect on resting heart rate and on maximum heart rate in a standard exercise test.

5 Pindolol tended to cause least change from placebo in resting spirometry, caused significant tremor response, inhibited the fenoterol airway response, and tended to protect against inhaled histamine.

6 Atenolol 50 mg was the only drug to allow a fenoterol airway response similar to placebo. Atenolol increased the inhaled histamine responsiveness.

7 Propranolol 160 mg caused the most reduction in spirometry but also tended to cause the maximum reduction in exercise heart rate. Propranolol caused increased inhaled histamine responsiveness.

8 Initial sensitivity to inhaled histamine did not necessarily predict significant reduction in an asthmatics' spirometry by a β -adrenoceptor antagonist. The effect of a β -adrenoceptor antagonist on histamine responsiveness does not correspond to its effect on inhaled β_2 -adrenoceptor agonist responsiveness.

Introduction

β -adrenoceptor antagonists have been known to aggravate asthma since 1964 (McNeill, 1964). There have been efforts to develop β -adrenoceptor antagonists which have fewer adverse respiratory effects than the non-selective agent propranolol. McDevitt (1978) criticized many of the clinical studies of the assessment of selectivity of the β -adrenoceptor antagonists. In particular he indicated that measurements of changes in resting airway function, failure to relate changes in cardiac response to changes in airway function, and the study of normal subjects, were all unsatisfactory techniques for the assessment of the relative airway effects of β -adrenoceptor antagonists.

The concept of a pure β_2 -adrenoceptor population in airway smooth muscle and a pure β_1 population in cardiac muscle has now been amended to a mixed

β -adrenoceptor population existing in these tissues (Lees, 1981). It is thought that the β -adrenoceptor subtypes in the same tissue may subserve the same function. These newer concepts make it even more difficult to interpret clinical data concerning cardioselectivity, unless the concept of airway smooth muscle containing mainly β_2 -adrenoceptors and cardiac muscle mainly β_1 -adrenoceptors is also accepted.

The present study was designed to fulfil the McDevitt (1978) criteria. β -adrenoceptor antagonist cardiac effects were assessed by the measurement of resting and exercise heart rate; respiratory effects were assessed by resting spirometry, response to a histamine inhalation test and spirometric response to inhaled fenoterol on each study day in each patient. Skeletal muscle tremor response, a β_2 -adrenoceptor

effect (Lees, 1981) was also measured. In addition six placebo studies per patient were included to enable confidence limits to be established for an individual's response. The effect of two dose levels of the non-selective β -adrenoceptor antagonist propranolol, the β_1 selective adrenoceptor antagonist atenolol, and the non-selective β -adrenoceptor agonist with partial agonist properties pindolol, were studied in a group of mild asthmatics.

Methods

Twelve asthmatic patients were selected to participate in the study (Table 1). These patients had mild to moderate asthma, with some patients requiring regular inhaled bronchodilator (patient 11 also took inhaled beclomethasone), and other patients developing asthma only in response to laboratory inhalation challenge. Each patient gave informed written consent and the protocol was approved by the local Ethics Committee. Patients who had renal, metabolic or cardiac disease, or smoked, or women not taking oral contraceptive tablets were excluded. All patients were classified as extrinsic asthmatics on the basis of seasonal symptoms, childhood onset of asthma, positive family history and skin prick tests. Studies were performed during the winter months when inhaled allergen exposure, except for house dust and the dust mite, was minimal. The patients had been on stable medications for 2 weeks, had no symptoms of a respiratory tract infection for at least 4 weeks, and had no relevant allergen exposure for at least 1 week. Prior to each study day patients abstained from in-

haled bronchodilators for at least 8 h and patient 11 continued her usual dose of inhaled beclomethasone. All studies were conducted in the late afternoon or evening with a minimum 3 day interval between study days. Baseline forced expired volume in one second (FEV_1) values were required to be within a $\pm 10\%$ range for the 12 study days. Patient 3 developed an upper respiratory tract infection during the study necessitating a delay in 6 weeks until her histamine response returned to the baseline established before the study.

The daily protocol (Figure 1) commenced at the same time of day for each patient. The study began with a 30 min rest period in the seated position. Heart rate was assessed by counting the pulse rate for 30 s;

Figure 1 Daily study protocol. FEV_1 = forced expired volume in 1 second; HIT = histamine inhalation test; Exercise = Stage I exercise test. Arrows indicate timing of treatment, blood sampling and measurements.

Table 1 Patient data

Patient	Age (years)	Height (cm)	Weight (kg)	Sex	Mean PC_{corr} (mg/ml)	Mean baseline FEV_1 (% predicted)*	Medications
1	26	167	74	F	0.66	113	S p.r.n.
2	25	156	60	F	7.23	124	Nil
3	24	157	57	F	0.36	95	S p.r.n.
4	28	165	66	F	2.12	89	Nil
5	21	170	68	F	1.69	87	S p.r.n.
6	26	154	54	F	2.34	108	S p.r.n.
7	37	164	64	F	0.23	79	S 200 & p.r.n.
8	22	171	64	F	3.36	125	S p.r.n.
9	28	181	66	M	4.60	97	Nil
10	34	173	61	F	5.57	98	Nil
11	23	158	53	F	1.55	87	S p.r.n., B 200
12	37	175	73	M	9.67	121	Nil

Definitions of abbreviations:

FEV_1 = forced expired volume in 1 second

S = inhaled salbutamol (μ g/day)

PC_{corr} = provocative concentration to cause an FEV_1 value 20% below the lowest placebo post-saline FEV_1 . Mean of 6 placebo days.

* Morris, Koski & Johnson (1971)

p.r.n. = as required, not daily

B = inhaled beclomethasone dipropionate, μ g/day

tremor was assessed by an observer using the method described by Ruffin *et al.* (1979). The best FEV₁ and maximum mid-expiratory flow rate (MMEF) from three satisfactory spirograms measured on a single breath bellows spirometer (Vitalograph®) were recorded. A venous blood sample was drawn and the patient then ingested 11 tablets in the double-blind, randomized, crossover, placebo controlled study. The effective drug doses on the 12 study days were: 6 placebo days; 40 mg and 160 mg propranolol; 50 mg and 200 mg atenolol; 5 mg and 20 mg pindolol. Heart rate, tremor and FEV₁ were measured at 30, 60 and 90 min after ingestion of the tablets. A further blood sample was taken and then a standardized histamine inhalation test was performed using a tidal breathing technique similar to that described by Cockcroft *et al.* (1977). Briefly, this consisted of using a Wright nebulizer driven by an airflow of 9 litres/min to generate an aerosol from 5 ml of histamine solution (mean output $\pm$ s.d. = 0.21 ± 0.02 ml/min). The patient inhaled the aerosol from a face mask by tidal mouth breathing for 2 min. FEV₁ values were then measured at 30 s, 90 s, and subsequently at minute intervals until the FEV₁ began to increase. A saline diluent control and then doubling concentrations of histamine were used until at least a 20% fall in FEV₁ was achieved. To allow for variation in the FEV₁ prior to the histamine inhalation tests, the provocative concentration of histamine required to cause an FEV₁ value 20% below the minimum placebo post-saline FEV₁ (PC_{corr}) was interpolated from a log dose-response curve (Ward *et al.*, in preparation).

At the completion of the histamine inhalation test each patient was allowed to recover spontaneously. When the FEV₁ had reached a value within 10% of the 90 min FEV₁ value a standard maximum progressive workload Stage I exercise test was performed on a bicycle ergometer (Jones *et al.*, 1975). Heart rate and ventilation were continuously monitored. Maximum heart rate, ventilation and workload were recorded and a further venous blood sample collected at the completion of the exercise test. When the patient's FEV₁ was within 10% of the value prior to the exercise test, successive doses of inhaled fenoterol 200 μ g, 200 μ g and 400 μ g were administered at 15 min intervals and the FEV₁, tremor and heart rate measured just before the next dose. An Aerochamber (Corr *et al.*, 1980) was used to provide a standardized administration mode for the fenoterol metered dose inhaler.

Plasma was separated from the venous blood sample and stored at -20°C for subsequent analysis. All drug assays were by high performance liquid chromatography with fluorescence detection after the drugs were extracted from plasma. Propranolol was extracted and assayed as described by McLean *et al.* (1980); atenolol was assayed by the method de-

scribed by Weddle *et al.* (1978); and pindolol was assayed by the method described by Bangah *et al.* (1980).

Drug-induced changes in FEV₁, heart rate and tremor were analysed at each time interval by analysis of variance and multiple range comparison test (Nie *et al.*, 1975). Similarly, maximum exercise heart rate, maximum exercise workload, maximum exercise ventilation and PC_{corr} were analysed for drug induced changes by an analysis of variance. Logarithmic transformations of PC_{corr} were made prior to analysis. 95% confidence limits for an individual patient's placebo response were established from the six placebo days. For six values in a two-tailed *t* distribution this requires a range of ± 2.75 s.d. from the mean (Sokal & Rohlf, 1960; Miller, 1966). Areas under the FEV₁ and tremor response curves for the baseline to 90 min period were calculated by the trapezoidal rule and differences between drug treatments analysed by analysis of variance. The areas under the mean FEV₁ and tremor response curves from 150 to 195 min were expressed as a percentage of the potential response using the mean placebo results of 165–195 min to calculate the potential area for each drug treatment. This was also done for individual results, as well as the group mean, to enable a statistical analysis. However, this technique for individuals may induce bias with small potential areas e.g. patient 12, 150–195 min FEV₁ potential area with pindolol 5 mg was 0.006 litre; the actual area was -0.063 litre h making the percentage of the potential area -1050% . Differences between the drug concentrations at 90 and 150 min were analysed by Student's paired *t*-test (Snedecor & Cochran, 1967).

Results

There was no significant difference in the mean baseline values of FEV₁ ($P > 0.99$), MMEF ($P > 0.99$), heart rate ($P > 0.99$) and tremor ($P > 0.70$) between study days (Table 2). No significant differences were found between the six placebo days for any measurement ($P > 0.05$). The mean changes from baseline FEV₁ (Figure 2) showed significant differences ($P < 0.05$) at: 60 min propranolol 160 mg < placebo, pindolol 5 mg, pindolol 20 mg; propranolol 40 mg < placebo; 90 min propranolol 160 mg < placebo, pindolol 20 mg; propranolol 40 mg < placebo; 165 min propranolol 160 mg < placebo, atenolol 50 mg; 180 min propranolol 160 mg < placebo.

Individual patients FEV₁ changes exceeding the mean ± 2.75 s.d. range during the first 90 min of that patient's six placebo days demonstrated a pattern which did not appear to be dependent on the drug

Table 2 Mean ($\pm$ s.d.) baseline values of FEV₁, MMEF, heart rate and tremor score

	FEV ₁ (l)	MMEF (l/s)	Heart rate (beats/min)	Tremor (arbitrary units)
Placebo	3.31 $\pm$ 0.75	3.45 $\pm$ 1.09	78 $\pm$ 17	0.5 $\pm$ 0.6
Propranolol 40 mg	3.25 $\pm$ 0.79	3.57 $\pm$ 1.21	77 $\pm$ 14	0.3 $\pm$ 0.5
Propranolol 160 mg	3.28 $\pm$ 0.85	3.50 $\pm$ 1.18	79 $\pm$ 19	0.5 $\pm$ 0.5
Atenolol 50 mg	3.33 $\pm$ 0.71	3.47 $\pm$ 1.12	80 $\pm$ 18	0.4 $\pm$ 0.5
Atenolol 200 mg	3.28 $\pm$ 0.78	3.31 $\pm$ 0.87	76 $\pm$ 17	0.3 $\pm$ 0.5
Pindolol 5 mg	3.29 $\pm$ 0.83	3.41 $\pm$ 1.05	78 $\pm$ 14	0.3 $\pm$ 0.5
Pindolol 20 mg	3.31 $\pm$ 0.77	3.39 $\pm$ 1.14	78 $\pm$ 13	0.3 $\pm$ 0.5

dose nor the patient's resting responsiveness to inhaled histamine (Table 3).

The area under the FEV₁ 90 min response curve (Table 4) showed that only propranolol 160 mg was significantly less than placebo. There was a trend for the non-selective agent propranolol, to cause a greater reduction in the resting FEV₁ response area than the β_1 -selective agent atenolol, and the non-selective agent with partial agonist properties, pindolol. Individuals falling below the mean -2.75 s.d. range were patient 2 for propranolol 160 mg, patient 6 for propranolol 40 mg, pindolol 20 mg; and patient 7 for propranolol 160 mg, atenolol 200 mg and atenolol 50 mg. The mean percentage of the potential response area under the FEV₁ 150–195 min curve (Table 4) shows a trend for the non-selective β -adrenoceptor antagonists to inhibit the fenoterol response in contrast to the β_1 -selective antagonist which in low dose enabled a response similar to placebo fenoterol response.

The mean changes from baseline MMEF (Figure 3) showed significant differences ($P < 0.05$) at: 60 min propranolol 160 mg, propranolol 40 mg $<$ pindolol 5 mg; 90 min propranolol 160 mg $<$ placebo; 165 min propranolol 160 mg $<$ placebo, atenolol 200 mg and atenolol 50 mg, propranolol

40 mg $<$ placebo, atenolol 50 mg; 180 min propranolol 160 mg $<$ placebo, atenolol 200 mg, atenolol 50 mg and pindolol 5 mg; 195 min propranolol 160 mg, propranolol 40 mg $<$ placebo, atenolol 50 mg.

Comparison of this data with that of the FEV₁ data suggests that the MMEF is more discriminatory than FEV₁ in assessing fenoterol responsiveness in the presence of β -adrenoceptor antagonists in mild asthmatics, but less so in the resting 0–90 min period.

The mean change in heart rate from baseline (Figure 4) has the following significant differences ($P < 0.05$) at:

60 min propranolol 160 mg, propranolol 40 mg, atenolol 200 mg $<$ placebo; 90 min propranolol 160 mg, atenolol 200 mg, atenolol 50 mg $<$ placebo; 150 min all active drugs $<$ placebo, propranolol 160 mg $<$ pindolol 5 mg; 165, 180 and 195 min propranolol 160 mg, propranolol 40 mg, atenolol 200 mg, atenolol 50 mg $<$ placebo; 165 and 180 min propranolol 160 mg $<$ pindolol 20 mg, pindolol 5 mg; 165 min atenolol 50 mg $<$ pindolol 5 mg.

The mean change in tremor from baseline (Figure 5) has the following significant differences ($P < 0.05$) at:

60 min propranolol 160 mg $<$ pindolol 5 mg and

Table 3 Individuals exceeding mean placebo ± 2.75 s.d. range for FEV₁ during 3 measurements in the 0–90 min period

Patient	Mean PC _{corr} (mg/ml)	Propranolol		Atenolol		Pindolol	
		160 mg	40 mg	200 mg	50 mg	20 mg	5 mg
1	0.66		xx	x			
2	7.23	x	x	x			
4	2.12		x		x		
6	2.34	x	xxx	x		xxx	I
7	0.23	xx	x	x	x	x	

Definition of abbreviations

x = less than mean -2.75 s.d. on one reading

xx = less than mean -2.75 s.d. on two readings

xxx = less than mean -2.75 s.d. on three readings

I = greater than mean $+2.75$ s.d.

PC_{corr} = provocative concentration to cause an FEV₁ value 20% below the lowest placebo post-saline FEV₁. Mean of 6 placebo days.

Figure 2 Mean changes from baseline of FEV₁ (forced expired volume in 1 second) at each measurement time for the 7 treatments (— placebo, —·— 20 mg pindolol, ——— 5 mg pindolol, ——— 160 mg propranolol, 40 mg propranolol, - - - 200 mg atenolol and ——— 50 mg atenolol).

pindolol 20 mg; 90 min placebo, propranolol 160 mg, atenolol 50 mg < pindolol 5 mg; 150 min propranolol 160 mg < pindolol 20 mg; 165 min propranolol 160 mg < placebo, pindolol 5 mg, pindolol 20 mg, atenolol 200 mg < pindolol 5 mg; 180 min propranolol 160 mg < placebo; 195 min propranolol 160 mg, propranolol 40 mg, atenolol 200 mg < placebo, propranolol 160 mg < pindolol 5 mg.

The mean percentage of the potential response area under the tremor 150–195 min curve (Table 4) shows that low and high dose propranolol and high dose atenolol tend to cause greater reduction in the induced tremor than both doses of pindolol and low dose atenolol. The mean maximum heart rate achieved during the exercise test (Table 5) showed that all active drugs < placebo; and propranolol 160 mg < atenolol 50 mg, propranolol 40 mg ($P < 0.05$). There were no significant differences between treatment days for maximum minute ventilation and maximum workload achieved during exercise ($P > 0.05$) (Table 5). However, there was a trend for larger doses of the active drugs to reduce the maximum achieved workload, more than the smaller doses.

The PC_{corr} geometric means (Table 5) show a trend for pindolol to increase the value as compared to

Table 4 Mean $\pm$ s.d. of areas under 0–90 min FEV₁ and tremor responses and mean values of % area under potential area response curves (150–195 min) for FEV₁ and tremor

Treatment day	Area under FEV ₁ 0–90 min response curve (litre. h)	Mean % area under FEV ₁ potential response 150–195 min (% placebo)		Area under tremor 0–90 min response curve (units. h)		Mean % area under tremor potential response 150–195 min (% placebo)	
		Calculated from mean group values	Calculated from individual patient values			Calculated from mean group values	Calculated from individual patient values
Placebo	–0.014* $\pm$ 0.105	100.0	100.0† $\pm$ 82.1	–0.045 $\pm$ 0.682	100.0	100.0 $\pm$ 157.0	100.0 $\pm$ 157.0
Propranolol 40 mg	–0.096 $\pm$ 0.104	52.7	58.2 $\pm$ 55.7	0.021 $\pm$ 0.617	24.9	18.5 $\pm$ 22.2	18.5 $\pm$ 22.2
Propranolol 160 mg	–0.142 $\pm$ 0.074	38.8	31.9 $\pm$ 50.1	–0.458 $\pm$ 0.602	24.6	16.6 $\pm$ 75.4	16.6 $\pm$ 75.4
Atenolol 50 mg	–0.060 $\pm$ 0.136	118.0	165.9† $\pm$ 175.0	–0.188 $\pm$ 0.575	57.5	63.9 $\pm$ 63.2	63.9 $\pm$ 63.2
Atenolol 200 mg	–0.063 $\pm$ 0.104	61.2	86.2 $\pm$ 50.1	0.021 $\pm$ 0.470	25.9	26.0 $\pm$ 25.6	26.0 $\pm$ 25.6
Pindolol 5 mg	–0.038 $\pm$ 0.091	49.5	–33.1 $\pm$ 330.7	0.354* $\pm$ 0.494	94.2	131.0 $\pm$ 160.6	131.0 $\pm$ 160.6
Pindolol 20 mg	–0.015 $\pm$ 0.093	38.6	50.7 $\pm$ 86.6	0.333* $\pm$ 0.587	44.6	115.0 $\pm$ 314.0	115.0 $\pm$ 314.0

* = significantly greater than propranolol 160 mg ($P < 0.05$)

† = significantly greater than pindolol 5 mg ($P < 0.05$)

Figure 3 Mean changes from baseline of MMEF (maximum mid expiratory flow rate) at each measurement time for the 7 treatments (— placebo, —. 20 mg pindolol, --- 5 mg pindolol, -.- 160 mg propranolol, 40 mg propranolol, -.-.- 200 mg atenolol and —•— 50 mg atenolol).

placebo, and propranolol and atenolol to reduce the value. This trend does not reach statistical significance ($P > 0.05$).

Examination of the individual PC_{corr} results (Table 6) show that many patients fall below the mean -2.75 s.d. (from the 6 placebo days) range for some of the active drugs. There appears to be little difference in the effect between propranolol and atenolol and there is no apparent dose dependent effect. Pindolol (20 mg) protected against histamine induced bronchospasm in patient 11.

The mean drug concentrations (Table 7) showed a trend for similar 90 and 150 min plasma propranolol concentrations ($P < 0.5$), pindolol to have 90 $>$ 150 min concentrations ($P > 0.1$), and atenolol 150 $>$ 90 min concentrations ($P > 0.1$). There was considerable interindividual variation in plasma drug concentrations which is demonstrated by the size of the s.d.

Figure 4 Mean changes from baseline of heart rate at each measurement time for the 7 treatments (— placebo, —. 20 mg pindolol, --- 5 mg pindolol, -.- 160 mg propranolol, 40 mg propranolol, -.-.- 200 mg atenolol, —•— 50 mg atenolol).

Discussion

The present study has shown that β -adrenoceptor antagonists, both non-selective and cardioselective, can lower expiratory flow rates in asthmatics, and that the level of responsiveness to inhaled histamine does not necessarily predict those patients likely to have an adverse airway response. In addition, the level of responsiveness to inhaled histamine in the presence of the β -adrenoceptor antagonist does not equate with the bronchodilator response possible in the presence of the antagonist.

The disadvantage of the present study design is related to the statistical group analysis of 7 treatment days. This disadvantage limits the sensitivity of the group data analysis and could only be improved by reducing the number of treatments and/or by increasing the number of patients. The advantages of the study design include the ability to determine an individual response with the establishment of a placebo range from six values. This placebo range could be reduced, and the analysis made more sensitive, by increasing the number of placebo days, but there has to be a balance between the theoretical ideal number of placebo days and the practical capabilities of patients. An individual assessment is important in asthma because of the variable nature of the condition. The present study design has other positive features with the assessment of cardiac, airway and skeletal

Figure 5 Mean changes from baseline of skeletal muscle tremor at each measurement time for the 7 treatments (— placebo, —. —. 20 mg pindolol, --- 5 mg pindolol, - · - · - 160 mg propranolol, 40 mg propranolol, - - - - 200 mg atenolol and —•— 50 mg atenolol).

muscle tremor on each study day and the assessments have been made under conditions of rest, and stress by histamine inhalation, maximal exercise test and sequential fenoterol inhalations. The use of two dose levels in this study of asthmatic patients appears to satisfy the criteria suggested by McDevitt (1978) for assessing β-adrenoceptor antagonist selectivity properties. The use of multiple placebo studies enabling individual assessment of drug effects provides an additional benefit over the study criteria suggested by McDevitt (1978). The use of percentage of potential areas under response curve at the 150–195 min period in this study allows correction for the effect of the test drug on the measurement at 150 min. This is not important during the 0–90 min period, particularly with FEV₁, where there are criteria of limited baseline variation before entry into a study day. In a similar way the use of the PC_{corr} value in this study allows a correction for the drug effect on the FEV₁ prior to the histamine inhalation test.

Previous single dose studies have produced variable results for the effect of β-adrenoceptor antagonists on airway function in the conditions described in this present study. Connolly & Batten (1970) showed that in a group of nine mild to moderate asthmatic subjects intravenous propranolol 10 mg produced a significant fall in airways conductance whereas alprenolol (a partial agonist) 10 mg did not. Perks *et al.* (1978) in a double-blind study in a group of 6 patients with labile airways obstruction showed that oxprenolol (partial agonist) 80 mg aggravated airways obstruction whereas atenolol 50, 100 mg did not. In 5 patients with reversible airways obstruction Benson *et al.* (1977) used a single-blind study to show that propranolol 100 mg and pindolol 5 mg caused significant decreases in FEV₁ whereas atenolol

Table 5 Mean ± s.d. values for exercise maximum heart rate, ventilation and workload, and geometric mean ± log₁₀ s.d. PC_{corr} values

	Maximum exercise heart rate (beats/min)	Maximum exercise minute ventilation (litres/min)	Maximum exercise workload (k.p.m.)	PC _{corr} (mg/ml)
Placebo	171.0 ± 16.6	68.9 ± 18.9	863 ± 297	2.00 (± 0.508)
Propranolol 40 mg	134.7 ± 12.9†*	59.5 ± 18.4	813 ± 270	1.08 (± 0.713)
Propranolol 160 mg	116.2 ± 10.6*	57.2 ± 14.5	625 ± 234	1.03 (± 0.578)
Atenolol 50 mg	135.8 ± 21.4†*	62.6 ± 19.8	817 ± 276	1.54 (± 0.619)
Atenolol 200 mg	122.8 ± 10.0*	56.4 ± 15.0	750 ± 202	1.03 (± 0.702)
Pindolol 5 mg	130.3 ± 10.3*	61.1 ± 18.4	800 ± 305	2.12 (± 0.538)
Pindolol 20 mg	125.5 ± 12.8*	56.4 ± 17.2	733 ± 293	2.46 (± 0.697)

Definition of abbreviations

* significantly less than placebo, $P < 0.05$

† significantly greater than propranolol 160 mg, $P < 0.05$

PC_{corr} provocative concentration to cause an FEV₁ value 20% below the lowest placebo post saline FEV₁. Mean of 6 placebo days.

Table 6 Individuals exceeding mean placebo ± 2.75 s.d. range for PC_{corr}

Patient	Mean PC _{corr} (mg/ml)	Propranolol		Atenolol		Pindolol	
		160 mg	40 mg	200 mg	50 mg	20 mg	5 mg
2	7.23	x	x				
3	0.36		x	x			
4	2.12	x	x				
5	1.69	x		x	x		
6	2.34	x	x	x			
7	0.23		x	x			
8	3.36			x	x	I	
11	1.55	x					

*Definition of abbreviations*x = less than mean -2.75 s.d.I = greater than mean $+2.75$ s.d.PC_{corr} = provocative concentration to cause an FEV₁ value 20% below the lowest placebo post saline FEV₁. Mean of 6 placebo days.

100 mg did not. A similar result in a single-blind study was described by Decalmer *et al.* (1978) and some of the subjects in that study were presumably those described by Benson *et al.* (1977). Singh *et al.* (1976) could not differentiate between the increased airway resistance caused by propranolol 80 mg, metoprolol 100 mg (β_1 -selective) and practolol 250 mg (β_1 -selective and partial agonist) in a group of 12 asthmatic patients. Beumer *et al.* (1978) showed that pindolol 15 mg caused less marked FEV₁ reductions than propranolol 80 mg in 16 asthmatic patients and similarly Frishman *et al.* (1979) showed that nine patients who developed bronchospasm with propranolol, did not do so with pindolol, either acutely or long term. Christensen *et al.* (1978) observed that the mean FEV₁ did not significantly alter in 20 asthmatics after pindolol 5 mg; however, there were large changes in two patients. Mattson & Poppius (1978) observed that pindolol 15 mg caused a marked reduction in FEV₁ in four asthmatics. There are a range of interpretations that have been placed on these resting results. It should be emphasized that these results may reflect different patient populations.

The use of histamine or methacholine provocation tests to show changes in responsiveness to these agents in the presence of β -adrenoceptor antagonists is not new. Zaid & Beall (1966) showed that intravenous propranolol (0.1 mg/kg) increased an asthmatic's sensitivity to the airway effects of subcutaneous methacholine. Ryo & Townley (1976)

compared the effects of propranolol 1 mg, and practolol 15 mg and 30 mg, given intravenously on the sensitivity to inhaled methacholine, in a group of 15 asthmatic patients. They observed that propranolol increased the sensitivity to inhaled methacholine, whereas practolol did not. Ruffin *et al.* (1979a) were unable to show any significant difference between propranolol 80 mg and metoprolol 100 mg in their effect on the sensitivity to inhaled histamine in 12 mild asthmatics.

The bronchial response to an inhaled β -adrenoceptor agonist, usually isoprenaline or salbutamol, has been used in many clinical studies. Decalmer *et al.* (1978), Thiringer & Svedmyr (1976), Ryo & Townley (1976) Mattson & Poppius (1978), Beumer *et al.* (1978) and Benson *et al.* (1977), have all shown that the non-selective β -adrenoceptor antagonists, with or without partial agonist properties, tend to prevent the inhaled bronchodilator airway response more than the β_1 selective antagonists, and more than placebo. Skinner *et al.* (1976) suggests that the bronchoconstriction in asthmatics from propranolol is readily reversed by salbutamol. Thiringer & Svedmyr (1976) have also examined the effects of β -adrenoceptor antagonists on isoprenaline-induced tremor. They observed that the β_1 -selective antagonists caused less inhibition of tremor than the non-selective drug propranolol.

The general effects of the β -adrenoceptor antagonists in the present study can be discussed according to

Table 7 Mean ($\pm$ s.d.) drug concentrations (ng/ml)

Time after ingestion (min)	Propranolol		Atenolol		Pindolol	
	160 mg	40 mg	200 mg	50 mg	20 mg	5 mg
90	203 $\pm$ 131	35 $\pm$ 25	736 $\pm$ 426	175 $\pm$ 122	116 $\pm$ 48	40 $\pm$ 18
150	205 $\pm$ 89	41 $\pm$ 18	907 $\pm$ 382	238 $\pm$ 100	94 $\pm$ 46	30 $\pm$ 11

the separate study phases. During the resting 0–90 min period the non-selective antagonist propranolol caused a dose dependent reduction in spirometry and the partial agonist, non-selective agent pindolol tended to produce spirometry levels similar to placebo. Atenolol tended to be intermediate between pindolol and propranolol. One interpretation of these trends is that the partial agonist properties of pindolol may have a role in maintaining resting airway function of asthmatics. This interpretation is consistent with the data from Frishman *et al.* (1979) and Beumer *et al.* (1978), but does not explain the results of Perks *et al.* (1978), Benson *et al.* (1977) and Mattson & Poppius (1978). The partial agonist properties of pindolol are well demonstrated by the development of tremor in the 0–90 min period, reflecting skeletal muscle β_2 -adrenoceptor stimulation. In view of pindolol showing some β_2 -agonist activity, it is interesting to see that the resting heart rate response (principally reflecting β_1 -adrenoceptor mediated effects) is intermediate between placebo and propranolol/atenolol. This trend may suggest that a β_2 -partial agonist effect is greater for pindolol than a β_1 -agonist effect.

The trend for the partial agonist to protect against inhaled histamine may be related to its agonist pharmacology. β_2 -adrenoceptor agonists such as salbutamol are known to provide protection against histamine induced bronchospasm (Casterline *et al.*, 1976). Both propranolol and atenolol caused similar enhancement of histamine responsiveness and this may suggest that histamine provocation tests are not useful in predicting selectivity of β -adrenoceptor antagonists. Ryo & Townley (1976) showed that practolol did not alter asthmatics sensitivity to inhaled methacholine and in view of the demonstrated increase in histamine sensitivity with atenolol in this study, would suggest that it is the partial agonist property of the β -adrenoceptor antagonist which is the important factor in protecting against an increase in sensitivity to inhaled histamine or methacholine. That is, cardioselectivity or β_1 -selectivity may not be important. If this is true then one must reconsider the interplay of β_1 and β_2 adrenoceptors in airway smooth muscle since the non-selective and β_1 -selective antagonists in the present study, and that described by Ruffin *et al.* (1979a), cause similar increases in sensitivity to inhaled histamine. An additional feature of acute changes in sensitivity to inhaled histamine is that this may allow the provocation of clinical asthma by other mechanisms, such as allergen, to occur more readily (Cockcroft *et al.*, 1979). It is important to remember that protection against histamine induced bronchospasm does not necessarily equate with bronchodilator effects. An example of this is the powerful protection an anti-histamine provides against histamine (Casterline & Evans, 1977) when it

is generally accepted that anti-histamines have little or no place in the treatment of asthma. A surprising observation was that the reduction in spirometry values for individuals by β -adrenoceptor antagonists was not totally predicted by the individual's responsiveness to inhaled histamine. That is, those subjects who were most sensitive to inhaled histamine were not those showing the most marked changes in resting spirometry.

The reduction in maximum heart rate was significant for all active drug doses. The extent of the reduction tended to be dose dependent for each of the β -adrenoceptor antagonists. Propranolol 160 mg caused the greatest mean reduction in maximum heart rate which was significantly lower than that achieved with propranolol 40 mg and atenolol 50 mg. The reduction in maximum exercise heart rate also tended to parallel the reduction in maximum workload achieved. Each class of β -adrenoceptor antagonist achieved significant cardiac β_1 -adrenoceptor blockade and there was a trend for propranolol 160 mg to cause a greater effect than other drugs. This trend must be remembered when comparing the cardiac and respiratory effects of the antagonists, because the ideal situation is to compare respiratory effects of equipotent doses for cardiac blockade. Thus, in this study one may predict that propranolol 160 mg will have more adverse respiratory effects than atenolol 200 mg and pindolol 20 mg because it tends to cause a greater cardiac effect.

The pattern of spirometry response to inhaled bronchodilator provides a different interpretation to that obtained for resting spirometry effects of the β -adrenoceptor antagonists. There is a clear advantage of the β_1 -selective antagonist atenolol, over the two non-selective drugs. This effect does appear to be dose dependent. That is, the advantage of atenolol enabling a good patient response to inhaled bronchodilator is less pronounced at higher doses. This observation is consistent with those made by Decalmer *et al.* (1978), Thiringer & Svedmyr (1976), Ryo & Townley (1976) and Beumer *et al.* (1978). It is interesting to note in this bronchodilator responsiveness phase of the study, that the partial agonist properties of pindolol do not cause a different effect from propranolol. This is in direct contrast with the effect on resting spirometry. That is, the partial agonist properties of a non-selective β -adrenoceptor antagonist are important with stimulation of β_2 -airway adrenoceptors in the resting state, but do not confer any advantage over the non-selective antagonist properties alone when considering reversibility of spirometry changes induced by a combination of exercise and β -adrenoceptor antagonists.

When the tremor response to fenoterol is examined it appears that the partial agonist properties of pindolol do make it different from propranolol in

the effect on skeletal muscle β_2 -tremor response to fenoterol. It is not clear whether this is related to a higher level of skeletal muscle tremor prior to the administration of fenoterol. The trend for atenolol 200 mg to cause a similar reduction in tremor to that caused by propranolol 40 and 160 mg suggests loss of β_1 -selectivity of atenolol at higher dosage. This observation differs from that made by Thiringer & Svedmyr (1976) using metoprolol 50 and 100 mg, because in the present study it is only the 50 mg atenolol dose which tends to cause less inhibition of fenoterol induced tremor than propranolol. It appears that the propranolol effect on tremor is independent of dose above 40 mg, since both 40 and 160 mg doses give comparable results.

It is possible that the differences in effects of propranolol and pindolol on airway smooth muscle and skeletal muscle indicates differences in receptor types and populations between airway smooth muscle and skeletal muscle.

This study suggests that histamine responsiveness

alone does not predict possible adverse airway effects to β -adrenoceptor antagonists. It also shows that reversibility of bronchoconstriction by a β -adrenoceptor antagonist does not equate with changes in histamine responsiveness caused by β -adrenoceptor antagonists. The study would suggest that if a β -adrenoceptor antagonist had to be used in an asthmatic patient than a β_1 -selective antagonist with a relevant degree of partial agonist activity would appear to be the optimum agent. The writers do not recommend the use of any current β -adrenoceptor antagonists in asthmatic patients.

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