BRONCHIAL AND CARDIAC β -ADRENOCEPTOR BLOCKADE – A COMPARISON OF ATENOLOL, ACEBUTOLOL AND LABETALOL

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- 1 Bronchial and cardiac β -adrenoceptor blockade have been compared in six normal subjects after three β -adrenoceptor antagonists. Single and double doses of atenolol (50 and 100 mg), acebutolol (100 and 200 mg) and labetalol (150 and 300 mg) were studied on separate occasions.
- 2 Salbutamol airway dose-response curves were obtained by measuring the airway response as the change in specific airway conductance (sGaw) after increasing doses of inhaled salbutamol. Bronchial β -adrenoceptor blockade was assessed after each drug as the dose of salbutamol needed to cause a 50% increase in sGaw (sGaw D50).
- 3 Cardiac β -adrenoceptor blockade was assessed after the same doses of each β -adrenoceptor antagonist, by measuring the percentage reduction in exercise heart rate from control, after exercise for 5 min at 70% of the subject's maximum work rate.
- 4 Atenolol 50 and 100 mg caused least bronchial β -adrenoceptor blockade and the greatest reduction in exercise heart rate.
- 5 Acebutolol 100 and 200 mg and labetalol 150 and 300 mg produced more bronchial β -adrenoceptor blockade than atenolol.
- 6 With this approach new β -adrenoceptor antagonists can be assessed without putting asthmatic patients at risk.

Introduction

β -adrenoceptor antagonists may produce airway narrowing in asthmatic patients by inhibiting the increased sympathetic drive to bronchial smooth muscle (McNeil, 1964). Although it is claimed that many new β -adrenoceptor blocking drugs are cardioselective, comparison has been difficult because of the lack of adequate methods to assess bronchial β -adrenoceptor blockade in man. In practice bronchial activity has usually been assessed in patients with asthma, which apart from carrying a certain risk, gives a qualitative rather than quantitative assessment. We described a method for measuring β -adrenoceptor blockade quantitatively in normal subjects, by carrying out airway dose-response studies

with an inhaled β -adrenoceptor agonist, salbutamol and measuring the displacement of the agonist dose-response curve after the β -adrenoceptor antagonist (Gribbin, Baldwin & Tattersfield, 1979). We have now applied this technique to two of the newer β -adrenoceptor antagonists atenolol and acebutolol and an α - and β -adrenoceptor antagonist, labetalol, combining it with a measurement of the reduction in exercise heart rate after the same dose of each drug to provide an assessment of cardiac β -adrenoceptor blockade. The drugs were assessed in six subjects studied previously with salbutamol dose-response studies after practolol, propranolol, and on three occasions control runs with no β -adrenoceptor antagonist (Gribbin *et al.*, 1979).

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Methods

Six healthy, non-smoking, non-atopic subjects took part. All gave informed consent for the study which was approved by the local ethical committee. Each study was carried out at the same time in the morning with the subject fasting and studies on the same

subjects were at least 7 days apart. Salbutamol dose-response studies were carried out after single and double doses of oral atenolol, acebutolol and labetalol on separate days (six studies in all) and exercise studies after the same dose of each drug on six further occasions. The tablets were not matched but the subjects were not told which drug or dose was being studied. This was known by the technician carrying out the measurements, so all sGaw readings and heart rate recordings were coded and read by an observer unaware of the code.

Salbutamol dose-response studies

Airway resistance (Raw) and thoracic gas volume (TGV) were measured in the body plethysmograph to obtain values for specific airway conductance (sGaw – the reciprocal of Raw corrected for lung volume). Ten readings were taken to obtain a mean sGaw measurement. After a baseline measurement of heart rate and sGaw subjects took the following drugs in random order on separate occasions – atenolol, 50 and 100 mg, acebutolol, 100 and 200 mg and labetalol, 150 and 300 mg. Heart rate and sGaw were repeated 2 h later (3 h for acebutolol). An inhaled salbutamol dose-response curve was then carried out by measuring sGaw 15 min after six increasing doses of inhaled salbutamol from specially prepared metered aerosols. The dose increased from 10 µg to a cumulative dose of 810 µg. Heart rate was measured before each dose of salbutamol and the study discontinued if heart rate exceeded 100 beats min⁻¹. If, when the results were analysed, there were not at least three points on the steep part of the dose-response curve the study was repeated with more appropriate doses of salbutamol.

Exercise studies

After resting for 5 min on an electrically braked cycle ergometer (Elema Schonander), steady state exercise was carried out for 5 min at 70% of the subject's previously determined maximum workload. The electrocardiogram was monitored and control heart rate recorded during the fifth minute of exercise. Identical exercise studies were then carried out 2 h (3 h for acebutolol) after each dose of the six β-adrenoceptor antagonists on separate occasions. Heart rate after each β-adrenoceptor antagonist was compared to control exercise heart rate during the fifth minute of exercise.

Analysis of results

Resting sGaw measurements on the same subject show minor fluctuations from day to day. Since this results in slight displacement of subsequent dose-

response curves all baseline results for each subject were corrected to a mean sGaw value and all points on the dose-response curve corrected by the same factor. This correction is only valid if the β-adrenoceptor antagonist does not change sGaw, so we tested the change in sGaw and TGV after each 3-adrenoceptor antagonist by Wilcoxon's paired rank test. Labetalol and atenolol caused a significant increase in sGaw so appropriate corrections were made to all points on the labetalol and atenolol dose-response curves.

A regression of sGaw on log cumulative salbutamol dose was calculated by the method of least mean squares and an analysis of covariance (Snedecor & Cochran, 1967) was performed on the slopes of all dose-response curves. None of the drugs caused a significant change in the slope of the dose-response curve, so we calculated a common slope for each subject. The log doses of salbutamol causing a 50% increase in sGaw (sGaw D50) after the β-adrenoceptor antagonist were compared by Student's *t* test. The maximum sGaw response for each subject was known from previous salbutamol dose-response studies with no β-adrenoceptor antagonists (Gribbin *et al.*, 1979).

Results

Apart from mild tremor and slight apprehension there were no significant side-effects from salbutamol. Vomiting occurred in 1 subject after labetalol (300 mg) and stopped the exercise study. There were no other important side effects after β-adrenoceptor antagonists.

Changes after β-adrenoceptor blockade (Table 1)

Mean baseline TGV was 4.53 ± 1.13 l and showed no significant changes after any β-adrenoceptor antagonist. Baseline sGaw values ranged from 1.09 to $2.67 \text{ s}^{-1} \text{ kPa}^{-1}$ with a mean value of $1.84 \text{ s}^{-1} \text{ kPa}^{-1}$. Both atenolol and labetalol caused a significant in-

Table 1 Change in sGaw and TGV 2 h after each β-adrenoceptor antagonist (3 h acebutolol) and before the salbutamol dose-response study

	ΔsGaw	P value*	ΔTGV
Atenolol 50 mg	+ 0.04	< 0.05	- 0.07
Atenolol 100 mg	+ 0.03		- 0.06
Acebutolol 100 mg	+ 0.01	NS	+ 0.01
Acebutolol 200 mg	- 0.01		+ 0.13
Labetalol 150 mg	+ 0.16	< 0.01	- 0.08
Labetalol 300 mg	+ 0.15		- 0.15

* Wilcoxon's test — using combined doses of each drug. None of the changes in TGV was significant.

crease in sGaw: 0.16 and 0.15 s⁻¹kPa⁻¹ for labetalol 150 and 300 mg, and 0.04 and 0.03 s⁻¹kPa⁻¹ for atenolol 50 and 100 mg.

Following the β -adrenoceptor antagonists mean sGaw D50 values for salbutamol (Table 2) were 28 μ g and 39 μ g for atenolol 50 and 100 mg; 50 μ g and 79 μ g for acebutolol 100 and 200 mg, and 42 μ g and 83 μ g for labetalol 150 and 300 mg. sGaw D50 was significantly higher after acebutolol 100 and 200 mg and labetalol 300 mg, than after atenolol 50 mg.

Exercise studies

In the control study mean heart rate was 163 beats min⁻¹ during the fifth minute of exercise. The percentage reduction in heart rate for each drug is shown in Table 3. The reduction in exercise heart rate did not differ significantly after atenolol 50 mg, acebutolol 100 mg and 200 mg. Compared with atenolol 50 mg, there was a greater reduction in exercise heart rate after atenolol 100 mg ($P < 0.01$) and a smaller reduction after labetalol 150 mg ($P < 0.02$) and labetalol 300 mg ($P < 0.05$).

Discussion

Classically, competitive antagonist drugs are compared by measuring the degree to which they displace the agonist dose-response curve. This approach has been used in man to assess cardiac β -adrenoceptor blockade by measuring the heart rate response to increasing doses of intravenous isoprenaline (Pateron *et al.*, 1970; Cleaveland, Rango & Shand, 1972). A similar approach to the assessment of bronchial β -adrenoceptor blockade has been attempted in patients with asthma by measuring the FEV₁ response to increasing intravenous doses of isoprenaline before and after β -adrenoceptor antagonists (Johnsson, Svedmyr & Thiringer, 1975; Thiringer & Svedmyr, 1976). However, unlike most normal subjects, asthmatic patients have resting sympathetic activity to their airways. Since this varies in amount, β -adrenoceptor antagonists cause unpredictable changes in airway calibre making subsequent bronchodilatation difficult to quantify. This baseline change in airway calibre causes an apparent shift in the dose-response curve, and also alters the airway response to the β -adrenoceptor agonist which varies

Table 2 Dose of salbutamol needed to produce a 50% increase in sGaw

Subject	Atenolol 50 mg	Atenolol 100 mg	Acebutolol 100 mg	Acebutolol 200 mg	Labetalol 150 mg	Labetalol 300 mg
1	26.6	127.8	30.9	50.4	90.7	279.8
2	9.2	16.1	20.4	11.7	6.2	22.1
3	27.5	36.3	85.9	135.5	29.7	153.7
4	32.4	32.4	90.3	278.2	73.6	63.1
5	45.5	51.3	37.9	112.9	26.4	31.6
6	44.7	30.4	89.1	100.0	171.1	177.8
Geometric mean	27.6	39.5	50.5	79.4	42.1	83.4
P*	—	NS	$P < 0.05$	$P < 0.02$	NS	$P < 0.05$

* Student's *t*-test on log mean values compared to atenolol 50 mg.

Table 3 Control exercise heart rate and percentage reduction in exercise heart rate after each β -adrenoceptor antagonist

Subject	Control heart rate on exercise	% reduction in exercise heart rate					
		Atenolol 50 mg	Atenolol 100 mg	Acebutolol 100 mg	Acebutolol 200 mg	Labetalol 150 mg	Labetalol 300 mg
1	138	23.9	34.8	20.3	23.9	23.9	16.7
2	180	32.2	39.4	16.7	28.3	8.9	15.0
3	170	32.4	44.1	26.5	38.2	11.8	—
4	185	27.0	35.1	29.7	37.8	10.8	24.3
5	155	22.6	35.5	22.6	22.6	16.1	16.8
6	150	20.0	20.0	10.0	4.0	10.0	12.0
Mean	163	26.4	34.8	20.9	25.8	13.6	16.9
s.d.	18	5.1	6.1	7.1	12.6	5.6	4.6
s.e. mean	7	2.1	3.3	2.9	5.2	2.3	1.9

with initial airway diameter (Benson, 1975).

In the present study there was no significant decrease in sGaw after any β -adrenoceptor antagonist, confirming the absence of resting sympathetic tone to normal bronchi (Richardson & Sterling, 1969; Tattersfield, Leaver & Pride, 1973). The lack of any increase in sGaw following acebutolol which has intrinsic sympathetic activity is similar to our findings with practolol (Gribbin *et al.*, 1979), and may reflect the reduced affinity of acebutolol for β_2 -adrenoceptors. The increase in sGaw after labetalol may be related to α -adrenoceptor blockade though this would be unlikely to cause bronchodilatation in normal subjects where there is little evidence of active α -adrenoceptor activity to the airways (Snashall, Boother & Sterling, 1978). Alternatively, it might reflect a reflex reduction in vagal tone to the airways following the systemic consequences of α -adrenoceptor blockade. The small increase in sGaw after atenolol may have been a chance finding but if not might again reflect a reflex response to cardiovascular changes.

The doses of β -adrenoceptor antagonists used in this study were those considered to have roughly equipotent β_1 -adrenoceptor blocking activity to propranolol 40 and 80 mg. Studies were carried out at a time after ingestion when maximal effects were to be expected (Cuthbert & Collins, 1975; Conway *et al.*, 1976; Martin, Hopkins & Bland, 1976). The results show that although the sGaw D50 values for salbutamol vary between subjects the method is sensitive to the dose-dependency of β -adrenoceptor blockade since for each drug the higher dose caused more bronchial β -adrenoceptor blockade and a greater reduction in exercise heart rate.

Reduction in exercise heart rate is an accepted method of assessing cardiac β -adrenoceptor blockade providing the exercise is strenuous enough to increase heart rate to 130 beats min^{-1} after placebo (Robinson *et al.*, 1966). It did not, however, provide an accurate quantitative measure of cardiac β -adrenoceptor blockade for various reasons. Doubling the dose of β -adrenoceptor antagonist produced only a small further reduction in exercise heart rate implying that the doses used were probably approaching the plateau of the dose-response curve for reduction in exercise heart rate as noted previously with propranolol (Coltart & Shand, 1970). The smaller reduction in heart rate after labetalol has been attributed to compensatory changes following α -adrenoceptor blockade of peripheral vascular receptors (Richards, Woodings & Maconochie, 1977). The maximum reduction in exercise heart rate also appears to be less with β -adrenoceptor antagonists with intrinsic sympathetic activity (McDevitt, 1977). This may explain the smaller reduction in heart rate with

acebutolol 100 mg, though acebutolol 200 mg may be a more appropriate equivalent dose to propranolol 40 mg (Wilcox, 1978). For these various reasons cardiac β -adrenoceptor blockade could not be assessed precisely enough to obtain an accurate cardioselectivity index.

Certain practical conclusions can however be drawn. Earlier studies in the same six subjects showed that sGaw D50 in the absence of any β -adrenoceptor antagonists was 20.4 μg (Table 1, Gribbin *et al.*, 1979). Although these control studies were performed prior to the present study and without placebo, later placebo controlled studies showed very similar values in the same subjects (Mackay *et al.*, 1981). In the present study, atenolol 50 mg and 100 mg showed least bronchial β -adrenoceptor blockade with a mean sGaw D50 of 28 and 39 μg . The same dose produced a large reduction in exercise heart rate and are those used in clinical practice. Acebutolol showed slightly more bronchial β -adrenoceptor blockade, particularly if 200 mg acebutolol with an sGaw D50 of 79 μg is in fact a more appropriate dose to compare with propranolol 40 mg. This is still considerably less than the sGaw D50 after propranolol 40 mg in our previous study which was 432 μg (Gribbin *et al.*, 1979). Labetalol is more difficult to assess because of the change in baseline sGaw but it appears to cause a similar degree of bronchial β -adrenoceptor blockade to acebutolol. Potentially its α -adrenoceptor blocking effect might be of value in asthma where there is more evidence of α -adrenoceptor activity (Snashall *et al.*, 1978), although in one study of mild asthma it caused neither bronchodilatation nor bronchoconstriction (Skinner, Gaddie & Palmer, 1975).

The relevance of our studies depends on the assumption that β -adrenoceptor antagonists will antagonize the endogenous sympathetic drive to asthmatic airways to the same degree that they antagonize inhaled β -adrenoceptor agonists in normal subjects. This assumption is difficult to prove but clinical studies of oral β -adrenoceptor antagonists in patients with asthma are in general agreement with our findings. Allowing for the different doses of drug used in different studies the fall in FEV₁ or sGaw has usually been least with practolol and atenolol, rather more after acebutolol and most after propranolol (Skinner, Palmer & Kerridge, 1975; Vilsvik & Schaanning, 1976; Benson *et al.*, 1978).

All β -adrenoceptor antagonists appear to cause some bronchial β -adrenoceptor blockade and even the most cardioselective, such as practolol, have caused bronchoconstriction in patients with asthma and need to be used with care (Powles, Shinebourne & Hamer, 1969; Waal-Manning & Simpson, 1971). Our approach allows bronchial β -adrenoceptor

blockade to be assessed quantitatively without putting patients at risk and it should identify the drugs most likely to cause problems in asthmatic patients. We suggest that new β -adrenoceptor antagonists are assessed by this technique prior to studies in patients.

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