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Beta-blockers in bronchial asthma: effect of propranolol and pindolol on large and small airways

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ABSTRACT In 11 asthmatic subjects the relative magnitude and the site of airway bronchoconstriction were compared after the oral administration of 40 mg of propranolol and 2·5 mg of pindolol and the magnitude and site of bronchodilation produced by 0·5 mg subcutaneous terbutaline were tested after pretreatment with propranolol and pindolol. Specific airway conductance (sGaw) and peak expiratory flow rate (PEFR), both believed to reflect changes in large airways, and capacity isoflow (Ciso-$\dot{v}$) and $\Delta\dot{V}max_{50}$, both believed to reflect changes in small airways, were determined before and after administration of placebo, pindolol, and propranolol. Treatments were given double blind and in random order. After the administration of propranolol we noted a significant bronchoconstrictive effect in the large airways (mean values of PEFR and sGaw, expressed as percentages of control values, decreased by 87·4% ± 13·2% and 43·3% ± 8·9%) and in the small airways (mean value of Ciso-$\dot{v}$ increased by 20·6% ± 4·7% and that of $\Delta\dot{V}max_{50}$ decreased by 50% ± 11·9% of control). By contrast, pindolol produced no significant effect on sGaw or PEFR but the tests of small airway function showed significant bronchoconstriction (mean values of Ciso-$\dot{v}$ increased by 12·9% ± 2·6% and those of $\Delta\dot{V}max_{50}$ decreased by 47·2% ± 9·2%). This action makes pindolol potentially dangerous in asthmatic patients. The bronchodilator action of terbutaline on large airways is diminished after the use of both propranolol and pindolol.

Information on the effects of β-adrenergic blocking drugs on respiratory function tests in asthmatic subjects has been reported,[1–3] but so far little information is available on the effects of β-adrenergic blocking drugs on the results of tests believed to reflect small airway function.

Bronchodilation is mediated through catecholamine stimulation of the β_2-receptors in the lung and β-adrenergic-blocking drugs can precipitate bronchoconstriction. It is generally believed that intrinsic sympathetic activity is desirable in a beta-blocker that has to be given to a patient prone to bronchoconstriction.[4,5] Non-selective β-adrenergic blockers, with or without intrinsic sympathetic activity, may lessen the bronchodilator effect of β_2-stimulants.[6]

This study was designed to compare the effects of oral propranolol (a drug with practically no intrinsic sympathetic activity) and pindolol (a drug with high intrinsic sympathetic activity) on large and small airways and to examine the bronchodilator effect of terbutaline in asthmatic patients previously treated with propranolol or pindolol.

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Methods

Eleven asthmatic subjects (four male, seven female) were studied after giving informed consent. The subjects were all adults (mean age in years 31 ± 8 SD) with asthma as defined by Scadding;[7] the mean duration of asthma was 7 ± 3·4 SD years. All had a baseline FEV_1 which was less than 70% of the predicted normal value[8] (mean 45·7 ± 15·1 SD) and were capable of an improvement in FEV_1 of more than 15% after inhalation of two puffs (250 μg) of terbutaline from a pressurised aerosol. Our patients were having treatment that included terbutaline 2·5 mg and theophylline 250 mg, both four times daily. None of the subjects had received corticosteroids or cromoglycate during the 15 days before the study. Bronchodilator drugs were discontinued for 12 hours before each experiment. All subjects were non-smokers and none had a recent history of upper respiratory tract infection. Seven patients were

judged to have extrinsic asthma on the basis of a history of atopy or positive reactions to cutaneous testing.

The forced vital capacity (FVC) and its subdivisions were measured with the use of a water-sealed spirometer. Slow vital capacity (VC) and expiratory reserve volume (ERV) were also determined with this spirometer. Thoracic gas volume (TGV) at functional residual capacity (FRC) and airway resistance (Raw) were measured with the use of a variable-pressure, constant-volume plethysomograph.[9 10] Residual volume was calculated by subtracting ERV from TGV. Specific airway conductance (sGaw) was calculated by dividing the reciprocopal of Raw by TGV. Total lung capacity (TLC) was calculated by adding FVC or VC (whichever was larger) to residual volume.

Peak expiratory flow rate (PEFR) was measured with a Wright peak flow meter. Maximal expiratory flow volume (MEFV) curves were obtained with the use of a rolling seal spirometer (Ohio 840) after inhalation of air and after seven minutes' inhalation of a helium-oxygen mixture (20% O_2 in 80% He). The results were recorded on a pen-driven *x-y* recorder (Hewlett-Packard, model 7041A) with an acceleration of 3000 in/s^2 on the *y* axis and 2000 in/s^2 on the *x* axis. Volume history was standardised by three inflations to total lung capacity before the performance of all MEFV curves. For both air and He-O_2 subjects performed multiple MEFV manoeuvres until three or more curves with similar slopes and VC within 2% of each other were obtained. The air and He-O_2 MEFV curves showing the best flow rates were then superimposed at TLC, and from the tracing maximal expiratory flows at 50% of VC ($\dot{V}max_{50}$) were calculated. From the same manoeuvres $\Delta\dot{V}max_{50}$ was also calculated from the formula[11]

$$\frac{\dot{V}max_{50}(He\text{-}O_2)-\dot{V}max_{50}\ (air)}{\dot{V}max_{50}\ air}.$$

The absolute volume of isoflow (Viso-$\dot{v}$) was calculated as the quantity between residual volume and the volume at which the He-O_2 and air curves first coincide.[12] The sum of the absolute Viso-$\dot{v}$ and residual volume was expressed as a percentage of the total lung capacity to obtain the capacity of isoflow (Ciso-$\dot{v}$).[13] Ciso-$\dot{v}$ takes into account changes in both residual volume (which would be expected to increase if obstruction in peripheral airways leading to trapping were made worse by treatment with a beta-blocker) and the volume of isoflow (which would also be increased if equal pressure points moved into small airways as a result of increase of airflow resistance in small airways).

The study was conducted on three separate days at least 48 hours apart. On the study day the subjects were under medical supervision for 24 hours. Early in the morning subjects underwent a control pulmonary function test consisting of whole-body plethysmography followed by timed spirometry, measurement of PEFR, and construction of maximal expiratory flow-volume curves obtained with subjects breathing air and the He-O_2 mixture. After completing the control studies the subjects were given a coded tablet (double blind) containing placebo, propranolol 40 mg, or pindolol 2·5 mg. The order of the treatments was randomly distributed. Peak flow rate measurements and standing heart rate counts were made every 30 minutes in the first three hours, and hourly for the following three hours. Pulmonary function tests were repeated two hours after administration of the drug, as peak concentrations in the blood and maximal beta-blockade are known to occur at about this time. Subsequently 0·5 mg of terbutaline was given subcutaneously and 30 minutes later the pulmonary function tests were repeated.

The effect of drug treatment on the density dependence of flow was measured in two ways: (1) as the difference between $\Delta\dot{V}max_{50}$ measured before (control values) and after beta-blocking treatment and after the administration of terbutaline and expressed as percentage of the control value; (2) as the difference between Ciso-$\dot{v}$ before and after beta-blocking treatment and after administration of terbutaline—this was also expressed as a percentage of the control value. The effect of drug treatment on large airway function was similarly obtained from changes in sGaw and PEFR.

Parametric data were analysed by Student's *t* test for paired data. A significant difference was assumed to exist for probability values $< 0·05$.

Results

The mean standing pulse rate before the administration of propranolol was 81·2 ± 5·3 beats/min and it dropped two hours after administration of propranolol to 62·5 ± 4·1; 30 minutes after subcutaneous terbutaline it was 63 ± 3·9 beats/min. The mean standing pulse rate before pindolol was 79·5 ± 4·5 per minute. It decreased after pindolol to 67·3 ± 3·8 beats/min and remained unchanged after subcutaneous terbutaline (68·0 ± 4·2 beats/min). Comparing the changes in heart rate after propranolol and pindolol we found no significant differences.

CONTROL PULMONARY FUNCTION

There were no statistically significant differences between the placebo, propranolol, and pindolol days

Table 1 *Baseline pulmonary function on the placebo, propranolol, and pindolol days (means ±SD)*

	Placebo	*Propranolol*	*Pindolol*
FEV_1 (l)	1·58 ± 0·80	1·57 ± 0·73	1·52 ± 0·67
FVC (l)	2·84 ± 0·83	2·84 ± 0·80	2·70 ± 0·80
PEFR ($l\,s^{-1}$)	4·21 ± 1·22	4·45 ± 1·12	4·12 ± 1·16
Raw ($kPa\,l^{-1}s^{-1}$)	0·71 ± 0·48	0·52 ± 0·40	0·62 ± 0·49
sGaw ($s^{-1}\,kPa^{-1}$)	0·87 ± 0·30	1·04 ± 0·40	0·97 ± 0·30
$\dot{V}max_{50}$ (air) (ls^{-1})	0·94 ± 0·46	1·01 ± 0·51	0·98 ± 0·49
$\Delta\dot{V}max_{50}$ (%)	39·6 ± 22	35·5 ± 19	40 ± 22
Viso-$\dot{v}$ (% VC)	28·1 ± 18·6	26·8 ± 11·3	24 ± 9·5
Ciso-$\dot{v}$ (% TLC)	63·2 ± 14·8	63·3 ± 11·9	62·7 ± 11·9
RV (l)	3·24 ± 1·40	3·01 ± 1·3	3·16 ± 1·5
TLC (l)	6·08 ± 1·44	5·86 ± 1·44	5·87 ± 1·44

FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; PEFR — peak expiratory flow rate; Raw — airway resistance; sGaw — specific airway conductance; $\dot{V}max_{50}$ — 50% of slow vital capacity (VC); Viso-$\dot{v}$ — absolute volume of isoflow; Ciso-$\dot{v}$ — capacity of isoflow; RV — residual volume; TLC — total lung capacity.

in any of the control pulmonary function measurements (table 1); pulmonary function was abnormal on all days.[8] Raw was increased and tests of expiratory airflow and sGaw were reduced. By comparison with our normal laboratory values of 51·9 ± 11·8%, mean $\Delta\dot{V}max_{50}$ was reduced. On the other hand, the volume of isoflow was significantly increased on all study days; our normal values were 13·7 ± 3·1% VC.

BRONCHOCONSTRICTIVE EFFECT OF PROPRANOLOL AND PINDOLOL

The changes in the physiological indices after placebo, propranolol, or pindolol are shown in table 2. Changes in Ciso-$\dot{v}$ and $\Delta\dot{V}max_{50}$ were in opposite directions and there was no quantitative correlation between the two measurements. A reduction in $\Delta\dot{V}max_{50}$ indicates bronchoconstriction, while the opposite is true for Ciso-$\dot{v}$. Mean decreases in $\Delta\dot{V}max_{50}$ after propranolol and pindolol were significantly greater than those observed with placebo ($p < 0·05$); the mean increase in Ciso-$\dot{v}$ was significantly greater with propranolol and pindolol ($p < 0·01$) than with placebo. The mean percentage increase in FRC after propranolol and pindolol was significantly greater than after placebo ($p < 0·05$ and $p < 0·01$ respectively). We also noticed a significant increase in RV after propranolol ($p < 0·05$) and pindolol ($p < 0·01$) by comparison with the RV changes after placebo.

Mean percentage decreases in sGaw and PEFR after propranolol were significantly greater than the changes observed after placebo ($p < 0·001$ and $p < 0·001$). In contrast, pindolol produced no significant decrease in sGaw or PEFR by comparison with placebo. We noted a bronchodilator effect after pindolol in one patient, although only the results of tests of large airway function were affected (PEFR and sGaw increased after pindolol by 21% and 55% respectively while Ciso-$\dot{v}$ increased by 28% and $\Delta\dot{V}max_{50}$ decreased by 16%).

EFFECT OF TERBUTALINE ON BRONCHOCONSTRICTION INDUCED BY PROPRANOLOL OR PINDOLOL

The changes are summarised in table 3.

The mean percentage increases in sGaw and PEFR were significantly greater ($p < 0·01$ and $p < 0·001$ respectively) when terbutaline was administered after placebo than after propranolol. The mean percentage increases in sGaw and PEFR were both significantly greater ($p < 0·01$) when terbutaline followed placebo than when it followed pindolol.

Ciso-$\dot{v}$ decreased after terbutaline administration and increased when terbutaline was given after propranolol or pindolol. These changes were

Table 2 *Effect of propranolol and pindolol on results of tests of small and large airways and on lung volumes (values expressed as percentage of control values on day of study)*

		Ciso-$\dot{v}$ (%)	*$\Delta\dot{V}max_{50}$ (%)*	*PEFR (%)*	*sGaw (%)*	*FRC (%)*	*RV (%)*
Placebo	mean	+ 1·9	+ 11·9	+ 4·6	+ 10·5	+ 1·2	+ 2·4
	SE	2·4	16·5	2·2	5·2	1·2	1·7
Propranolol	mean	+ 20·6†	− 50*	− 87·4‡	− 43·3‡	+ 14·1*	+ 16·2*
	SE	4·7	11·9	13·2	8·9	4·4	5·7
Pindolol	mean	+ 12·9†	− 47·2*	− 2·09 (NS)	− 8·7 (NS)	+ 7·1†	+ 10·5†
	SE	2·6	9·3	3·3	9·1	1·1	2·3

Significantly different from percent change after placebo: * = $p < 0·05$; † = $p < 0·01$; ‡ = $p < 0·001$ (paired data); NS = not significant
FRC — function residual capacity; for other abbreviations see table 1.

Table 3 *Effect of terbutaline on results of tests of small and large airways and on lung volumes* before and after a single dose of propranolol or pindolol*

Drug	*Ciso-$\dot{v}$ (%)*	*$\Delta\dot{V}max_{50}$ (%)*	*PEFR (%)*	*sGaw (%)*	*FRC (%)*	*RV (%)*
Placebo and terbutaline						
mean	− 12·3	+ 148	+ 34·1	+ 342·3	− 7·9	− 11·2
SE	4·6	98·1	5·9	108·0	2·9	4·2
Propranolol and terbutaline						
mean	+ 13·0‡	− 25·8 (NS)	− 10·4‡	− 29·9†	− 1·1 (NS)	− 2·4 (NS)
SE	4·6	23·3	3·03	10·3	1·3	2·8
Pindolol and terbutaline						
mean	+ 2·6*	− 12·3 (NS)	+ 5·2†	+ 57†	− 3·7 (NS)	− 2·2 (NS)
SE	3·02	16·6	4·8	33·4	1·9	3·6

Changes produced expressed as percentage of control values (= $p < 0{\cdot}05$; † = $p < 0{\cdot}01$; ‡ = $p < 0{\cdot}001$; NS = not significant).
For abbreviations see tables 1 and 2.

significant (table 3). The mean percentage changes in $\Delta\dot{V}max_{50}$ values were not significantly greater when terbutaline followed placebo than when it followed propranolol or pindolol.

An increase in FRC and RV that was produced by the administration of terbutaline after pindolol or propranolol was not significantly different from the FRC and RV changes that occurred when terbutaline was given after placebo.

Although increases in large and small airway resistance were recorded, no patient reported a major change in breathing after taking beta-blockers.

Discussion

The standing pulse rate was chosen to assess beta-blockade since this is influenced more by sympathetic and less by vagal discharge than is the supine pulse rate.[14] There was a mean decrease of about 19 beats per minute during propranolol treatment and about 12 beats per minute during pindolol treatment; it is difficult to judge whether the difference is due to a relatively higher dosage of propranolol or to the intrinsic sympathetic activity of pindolol. The doses of the drugs were chosen on the basis of accepted beta-blocking potency ratios in man and also because they were close to dosage levels used in clinical practice.[15]

Propranolol reduced sGaw and peak expiratory flow rate significantly but pindolol did not. The significantly greater deterioration in functional indices reflecting changes in large airway calibre after propranolol than after a beta-blocker with high intrinsic sympathetic activity has been referred to by others.[3,16] Although the helium isoflow volume and the ratio of MEFR with helium to MEFR with air are very poorly reproducible in normal subjects,[17] the deterioration in Ciso-$\dot{v}$ and $\Delta\dot{V}max_{50}$ after pindolol and propranolol in the present study was combined with a significant increse in FRC and RV. This is probably another manifestation of the degree of obstruction within the distal bronchi. Tests of small airway function seem to be required to identify the bronchoconstrictive effect of pindolol in asthmatic subjects.

Terbutaline's bronchodilating effect on large airways was significantly diminished when patients were pretreated with a single dose of propranolol or pindolol. It is difficult to comment on the effect of terbutaline in small airways of patients pretreated with a single dose of propranolol or pindolol since only the Ciso-$\dot{v}$ changes were significant.

Although pindolol has a high intrinsic sympathetic activity and has no detectable effect on the results of tests of large airway obstruction, it has a bronchoconstrictive effect on small airways similar to that of propranolol and thus may not be safe for the asthmatic patient. The bronchodilator action of the β_2-stimulant terbutaline on large airways is diminished after pindolol as well as after propranolol.

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