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Effect of selective and non-selective beta blockade on pulmonary function and tracheobronchial mucociliary clearance in healthy subjects

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ABSTRACT A controlled, double blind, crossover study was carried out to ascertain the effect of single doses of selective (100 mg atenolol) and non-selective (160 mg propranolol) beta blocker on pulmonary function and tracheobronchial mucociliary clearance. The study group comprised 12 healthy, young subjects. Adequate and comparable blockade was achieved with both drugs, the administration of which resulted in significantly lower pulse rates (at least up to eight hours after administration of the drug) and systolic blood pressures (three hours after drug administration) than were found with placebo. Small (of the order of 5%) but nevertheless statistically significant falls in FEV_1 and forced vital capacity accompanied the administration of both beta blockers (but not the placebo) and were measurable up to eight hours after administration of the drug. Indices of pulmonary function had returned to normal by the next day. Peak expiratory flow and indices of small airways function remained unaltered after beta blockade. Mean tracheobronchial mucociliary clearance was depressed after administration of both beta blocking drugs, although the reduction was significant ($p < 0.05$) only when propranolol was compared with placebo.

Tracheobronchial mucociliary clearance is one of the lungs' non-specific host defence clearance mechanisms. It can be altered by physical factors (such as exercise), environmental pollutants, disease, and pharmacological intervention.[1] Its control is not well understood. Circulating catecholamines may, however, have a role in the control of mucus transport since the β_2 adrenergic drug terbutaline given either subcutaneously[2] or orally[3] to healthy subjects has been reported to result in an increased clearance, though this has been disputed.[4 5] Orciprenaline when given to healthy subjects showed a regional effect on tracheobronchial mucociliary clearance.[6] Adrenaline, isoprenaline, and fenoterol[7 8] given topically (by aerosol) have given rise to enhanced tracheobronchial mucociliary clearance in healthy subjects. In patients with chronic bronchitis and asthma β agonists tend to enhance clearance.[9]

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The effect of beta blockers on tracheobronchial mucociliary clearance in man is not well documented. It is well known, however, that beta blockers may precipitate asthma in susceptible subjects.[10] To our knowledge the effect of beta blocking agents on tracheobronchial mucociliary clearance in health has not hitherto been studied. We report a study on the effect of non-selective and selective beta blockade on pulmonary function indices and tracheobronchial mucociliary clearance in 12 healthy subjects.

Mean (SD) physical characteristics and pulmonary function indices for 12 healthy subjects

M:F	6:6
Age (y)	25 (6)
Height (m)	1.70 (0.03)
Weight (kg)	68 (13)
FEV_1 (% pred[11])	125 (16)
FVC (% pred[11])	117 (15)
PEF (% pred[11])	101 (9)
FEF_{25-75} (% pred[11])	113 (22)
$\dot{V}max_{50}$ (% pred[12])	106 (21)
$\dot{V}max_{25}$ (% pred[12])	115 (32)

FVC—forced vital capacity; PEF—peak expiratory flow; FEF_{25-75}—maximum mid expiratory flow; $\dot{V}max_{50}$, $\dot{V}max_{25}$—flow rates at 50% and 25% of vital capacity; % pred—percentage of predicted value.

Methods

SUBJECTS

Twelve healthy volunteers took part in the study. Their physical characteristics and pulmonary function indices (means and standard deviations) are shown in the table. Six subjects (four female) were non-smokers and the remaining six subjects (two female) were current cigarette smokers with a mean (SD) tobacco consumption of 5.1 (8.4) pack years (one pack year = 20 cigarettes a day for one year). The subjects were selected for the study provided that they had normal pulmonary function and satisfactorily completed a medical questionnaire directed towards past symptoms of chest disorder. Informed written consent was obtained from all the subjects.

STUDY DESIGN

A controlled, double blind, crossover study (using the double placebo technique) was carried out. The subjects were studied on three occasions at intervals of one week. At each of the three assessments, which followed a 10 minute rest period, the subjects' pulse rate, blood pressure, and pulmonary function were measured. The subjects were then given, in a randomised manner, two tablets to take with a cup of water; the three treatments were (*a*) one placebo tablet and another containing 160 mg of propranolol, (*b*) one placebo tablet and another containing 100 mg of atenolol, and (*c*) two placebo tablets. The subjects (who were all employees of this hospital) were then allowed to proceed with their normal duties. Two hours after the medication their pulse rate, blood pressure, and pulmonary function were once again measured and immediately afterwards they inhaled the test radioaerosol for assessing tracheobronchial mucociliary clearance. Pulse rate and blood pressure were measured again one, three, six, and 24 hours after inhalation of the radioaerosol. Pulmonary function was assessed six and 24 hours after inhalation of radioaerosol, thus ensuring that the forced expiratory manoeuvres did not alter tracheobronchial clearance in the initial six hour period.

PULMONARY FUNCTION, PULSE RATE, AND BLOOD PRESSURE MEASUREMENTS

A Vitalograph spirometer was used to measure FEV_1, forced vital capacity (FVC), and maximum mid expiratory flow (FEF_{25-75}). Peak expiratory flow (PEF) was measured with a Wright peak flow meter. The flow rates at 50% and 25% ($\dot{V}max_{50}$ and $\dot{V}max_{25}$) of vital capacity (that is, remaining to be exhaled) were determined from maximal expiratory flow-volume (air) curves obtained with an Ohio 840 piston-cylinder type spirometer connected to a Bryans X-Y recorder. For all pulmonary function indices the highest reading out of three technically acceptable attempts was recorded.

Measurements of pulse rate and blood pressure were carried out by the same observer (AM L-J) after the subject had rested for 10 minutes; they always preceded any pulmonary function tests.

TRACHEOBRONCHIAL MUCOCILIARY CLEARANCE

For measurement of tracheobronchial mucociliary clearance[13] polystyrene particles were labelled[14] with technetium 99m and inhaled in eight breaths, each of 0.45 l, from functional residual capacity (FRC) with a three second breath hold. Mean inspiratory flow was recorded by a UV recorder from a pneumotachygraph. An initial deposition count of lung radioactivity was taken immediately after inhalation by twin, horizontally opposed anterior-posterior scintillation counters,[15] with wide angle lead collimators; further counts were made hourly for six hours with a final count at 24 hours. The 24 hour retention was taken to represent "alveolar deposition", that is

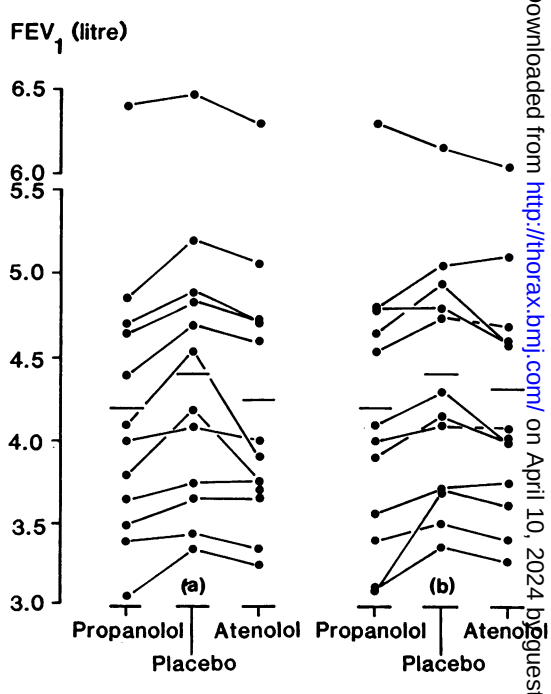

Fig 1 *Individual and mean (—) values of FEV_1 for 12 healthy subjects (a) two hours and (b) eight hours after administration of placebo, propranolol (160 mg), and atenolol (100 mg). At both times the results after propranolol and the results after atenolol are significantly different from those after placebo ($p < 0.01$).*

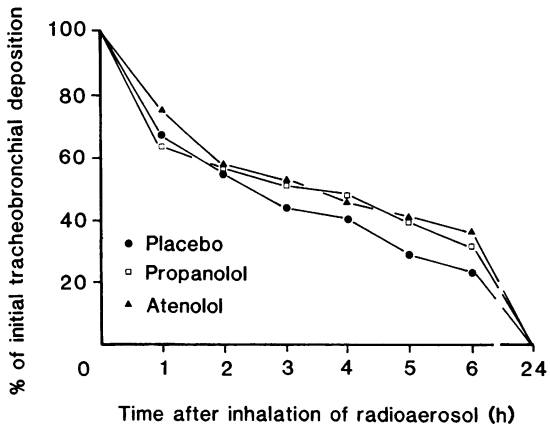

Fig 2 *Mean tracheobronchial clearance curves for 12 healthy subjects after placebo, propranolol (160 mg) and atenolol (100 mg) given two hours before the inhalation of the radioaerosol.*

radioaerosol unavailable for clearance via the mucociliary escalator.[16]

A gamma scanner[17] was used to obtain a quantitative index of initial deposition, the penetration index (PI); this was derived as the ratio of the amount of ^{99m}Tc activity present in an outer region of the right lung relative to that in an inner region. This index attempts to measure the extent to which the radioaerosol particles are distributed towards the periphery of the lungs.

The smokers did not smoke for one hour before or during the six hour tracheobronchial mucociliary clearance observation period.

STATISTICAL ANALYSIS

The Friedman two-way analysis of variance by ranks and the Wilcoxon test for pair differences were used to analyse the data.

Results

PULMONARY FUNCTION, PULSE RATE, AND BLOOD PRESSURE

Figure 1 shows the individual FEV_1 values for the study group (*a*) two hours and (*b*) eight hours after the administration of propranolol, placebo and atenolol. At both times observations after propranolol, atenolol, and placebo were significantly different (at two hours $\chi_r^2 = 16.73$ ($p < 0.005$); at eight hours $\chi_r^2 = 9.48$ ($p < 0.01$)). At both times FEV_1 was significantly ($p < 0.01$) lower with both beta blocking drugs than with placebo (mean (SEM) FEV_1 after placebo, propranolol, and atenolol: 4.4 (0.3), 4.2 (0.4), and 4.25 (0.3); 4.4 (0.2), 4.2 (0.3), and 4.3 (0.2) l at two and eight hours respectively). Similar small but nevertheless significant falls in FVC were noted for the same time intervals. By 24 hours after treatment the differences in FEV_1 and FVC between the effects of the beta blockers and those of the placebo were no longer significant. None of the other pulmonary function indices (that is, PEF, FEF_{25-75}, $\dot{V}max_{50}$ and $\dot{V}max_{25}$) showed any differences between medication with either drug and with placebo.

There was a significant fall in pulse rate after both beta blockers by comparison with placebo, which lasted for eight hours after administration. Systolic blood pressure also fell with both drugs (for propranolol $p < 0.05$; for atenolol $p < 0.01$), but diastolic pressure was reduced only with atenolol during the first three hours.

TRACHEOBRONCHIAL MUCOCILIARY CLEARANCE

The means (SE) of the average inspiratory flow rates after placebo, propranolol, and atenolol were 25 (1), 30 (3), and 28 (3) 1 min^{-1} ($\chi_r^2 = 3.79$, $p < 0.10$). The mean (SE) penetration indices were similar: 0.64 (0.05) with placebo, 0.66 (0.05) with propranolol, and 0.66 (0.06) with atenolol. The similarity in penetration indices was supported by the similar mean (SE) alveolar depositions attained in the three runs: 62% (4%) with placebo, 58% (5%) with propranolol, and 57% (3%) with atenolol.

Figure 2 shows the mean tracheobronchial mucociliary clearance curves obtained with placebo, propranolol, and atenolol. The mean clearance curves appear similar over the first two hours, thereafter diverging with both beta blocker drugs and showing a slower clearance than was found with placebo. The curves were analysed by comparing (*a*) the areas under the individual curves for two time intervals: 0–3 hours and 3–6 hours after inhalation of radioaerosol (the smaller the area the faster the mucociliary clearance) and (*b*) the percentages of radioaerosol retained at hourly intervals. The areas under the curves were calculated by the trapezoidal rule. There was no significant difference between the areas under the three curves for 0–3 hours. For 3–6 hours, however, there was a significant difference ($\chi_r^2 = 6.17$, $p < 0.05$), indicating slowing (that is, increase in the areas under the curves) of lung clearance with both beta blockers. The Wilcoxon test for paired differences in the areas under the curves for 3–6 hours between the placebo and drug runs indicated a significant ($p < 0.02$) slowing of mucociliary clearance after propranolol only by comparison with placebo. This difference was also evident from the radioaerosol retained at three hours ($p < 0.05$), four hours ($p < 0.02$), and five hours ($p < 0.05$). The difference

between atenolol and placebo approached significance ($p < 0.10$) at four and five hours only.

Discussion

A similar degree of beta blockade was achieved after the administration of 160 mg of propranolol and 100 mg of atenolol. Both drugs resulted in significant falls in FEV_1 and FVC of 5%, lasting for eight hours, returning to normal by 24 hours. These reductions were, however, so small as to be of no clinical consequence for this healthy group. The other pulmonary function indices (including those predominantly reflecting function of the small airways), were, surprisingly, unaltered.

Results of measurement of tracheobronchial mucociliary clearance are influenced to an important extent by the initial site of radioaerosol deposition. Proximal deposition gives rise to apparently faster clearance than does distal deposition in the lungs.[18] Factors that affect the initial topographical distribution of aerosol in the lung are: (*a*) the physical properties of the radioaerosol (*b*) the mode of inhalation, and (*c*) airway patency.[19 20] In this study (*a*) and (*b*) were similar for all three runs; (*c*), however, was slightly different between runs since FEV_1 and FVC were reduced after propranolol and atenolol. Nevertheless, the two indices of initial topographical distribution—alveolar deposition and penetration index—were virtually identical in the three runs, so that the tracheobronchial mucociliary clearance curves could be compared directly.

The Friedman two way analysis of variance by ranks indicated a significant ($p < 0.05$) slowing of tracheobronchial mucociliary clearance after beta blockade during the period three to six hours after radioaerosol inhalation—that is, from five to eight hours after the administration of the drug. Although on average the degree of slowing was similar with the two drugs, when they were compared with placebo statistical significance ($p < 0.02$) was attained only with propranolol. In general, the initial part (0 to about 3 hours) of the clearance curve represents mucociliary clearance of deposited radioaerosol from the proximal ciliated airways, whereas the later part (that is, about 3–6 hours) is taken to represent removal of radioaerosol from the more distal ciliated airways.[21] This study indicated a 32% increase on average in the areas under the curves for 3–6 hours (that is, slowing of mucociliary clearance distally) in healthy subjects after a single dose of a selective ($p < 0.10$) or a non-selective ($p < 0.02$) beta blocker.

Efficient tracheobronchial mucociliary clearance depends on the integrity of the ciliated epithelium, ciliary beat frequency, and coordination, the thickness and consistency of the periciliary layer, and the physicochemical properties and quantity of the epiphase. With in vitro experiments in animals low concentrations of propranolol (0.1 μmol/l) have been shown to block the cilioexcitatory effect of beta agonists. On the other hand, similar concentrations of propranolol (in the absence of beta agonists) have been reported to show no effect on ciliary activity.[22] High concentrations of propranolol (100 μmol/l) do decrease ciliary beat frequency, possibly owing to the local anaesthetic properties of the drug. The role of sympathomimetic agents on airway mucus secretions in man appears to be a matter of debate.[23–25] Both α and β adrenergic agents have been shown, in animal studies, to increase mucus glycoprotein and/or ion and water transport into the lumen of the airways.[26] Chopra and colleagues[27] reported that the intravenous administration of 3–5 mg propranolol hydrochloride to lightly anaesthetised dogs did not alter tracheal mucus velocities measured 15 minutes afterwards. In the only studies carried out in man Matthys *et al*[28] administered 20 mg of pindolol daily for three days to seven patients with chronic bronchitis and reported a retardation in mucociliary clearance rates. Dorow *et al*[29] gave propranolol 40 mg twice daily to six subjects with coronary heart disease (and normal lung function) and observed significantly slower mucociliary clearance than with placebo.

Impairment of mucociliary clearance has been shown to precede atelectasis[30] and has been implicated in the development of chronic airway obstruction.[31] Our observations have shown that single doses of selective and non-selective beta blockers can cause reduced pulmonary function and mucociliary transport in healthy subjects. This raises the question of what effect they may have in long term administration to patients who have cardiovascular disease without accompanying airways dysfunction.

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