Bronchodilator action of inhaled fenoterol and ipratropium in normal subjects: a teaching exercise for medical students

R. G. TAYLOR¹, JENNIFER MACLAGAN² & D. G. COOK³

Department of ¹Physiology, ²Pharmacology, and ³Clinical Epidemiology and General Practice, Royal Free Hospital School of Medicine, London NW3 2PF

1 A pharmacology practical class for preclinical medical students was designed as a placebo-controlled, double-blind trial of two bronchodilator drugs.

2 Fenoterol hydrobromide (800 µg), ipratropium bromide (80 µg) and placebo (propellant only) were given by metered dose inhaler to 79 non-asthmatic volunteers. Their effects on FEV₁, heart rate and tremor (assessed by the time taken to thread five sewing needles) were compared.

3 Both drugs caused a significant increase in FEV₁: the largest group mean increase was 77 ml, recorded 15 min after fenoterol, and 103 ml, recorded 60 min after ipratropium.

4 Fenoterol also caused a mean increase of 8.7 beats min⁻¹ in heart rate, 5 min after inhalation. This effect was still apparent after 60 min.

5 Fenoterol appeared to prolong needle threading time in some individuals.

6 In subjects who inhaled fenoterol, there were no correlations between the increase in FEV₁, the increase in heart rate, or the development of tremor.

7 It is concluded that inhaled fenoterol and ipratropium both cause bronchodilation in normal subjects. Systemic absorption of fenoterol is indicated by the rapid increase in heart rate. The bronchodilator effect of ipratropium suggests that resting airway calibre is governed partly by parasympathetic tone in normal subjects.

8 The bronchodilator and systemic effects of these drugs can be used to demonstrate pharmacological, therapeutic and statistical principles to medical students.

Keywords bronchodilators normal subjects student practical

Introduction

A pharmacology practical class for preclinical medical students was designed which illustrated the basic principles involved in carrying out a double-blind trial, had direct clinical relevance and brought together several disciplines within the medical school.

The effects of two inhaled bronchodilator drugs, fenoterol hydrobromide and ipratropium

bromide, were compared with those of placebo. The students made observations on themselves and analysed the results later in their statistics course. This introduced, in an interesting way, the controlled clinical trial based on objective assessment, the correct use of metered dose inhalers, and the fact that inhaled drugs may have systemic effects.

Methods

Subjects

Forty-seven male and 32 female second-year medical students volunteered to take part; 12 students did not participate because they were absent, recovering from minor illnesses, or unwilling to inhale the drugs. Four students with asthma were also excluded. Those who took part were all aged about 20 years, apart from six mature students all aged less than 30 years. The study was approved by the medical ethics committee, and a medically qualified member of staff was present throughout.

Drugs

Randomisation was arranged so that a third of the class took each drug. Metered dose inhalers were identical in appearance and the study was blind. Twenty-six took fenoterol hydrobromide (200 µg/puff), 26 took ipratropium bromide (20 µg/puff) and 27 took placebo (propellant only; this was identical to that used with fenoterol and ipratropium, and consisted of freons 11, 12 and 114, with soya lecithin surfactant). Under supervision, each student inhaled four puffs using the correct technique (Newman *et al.*, 1981a), having first practised with a placebo inhaler of a different shape.

Measurements

Baseline measurements were made before inhalation and the measurements were repeated 5, 15, 30, 45 and 60 min afterwards. Bronchodilatation was assessed by measuring forced expiratory volume in one second (FEV₁) with a Vitalograph spirometer. Three attempts were made and the largest volume obtained was recorded directly from the instrument in millilitres (BTPS). Heart rate was measured in beats min⁻¹ by counting the radial pulse. Tremor was assessed by measuring the time taken to thread five sewing needles mounted on a cork while seated with the arms unsupported.

Statistical analysis

The students analysed their own results in a subsequent 1 h practical class under the supervision of a statistician. The data were given to them as graphs similar to Figures 2, 4 and 6, but without any confidence limits drawn, and as the standard deviation and standard error of the baseline measurements and the standard error of the mean differences from the baseline values.

The students worked in groups of three, and each person was asked to carry out the following calculations for one only of FEV₁, heart rate and tremor: (1) calculate 95% confidence limits for the change from baseline at 60 min separately for each treatment group, and plot them on the graph; (2) determine whether there was a significant change in the placebo group; (3) using Student's *t*-test (two-tailed), determine whether the change at 5 min after inhaling either of the active treatments was significantly different from the change in the placebo group. Each group was asked to summarise its findings and to explain them in terms of the pharmacological action of the drugs and learning effects in the subjects. A class discussion was held at the end, when both a medical statistician and a pharmacologist were present.

In this paper, the differences between groups were compared using the maximum recorded increases in FEV₁, heart rate and needle threading time, using Student's *t*-test. The maximum increases were the largest that occurred in each individual subject, irrespective of how long after inhaling the drug they occurred. For subjects whose values after inhaling the drug were always lower than the baseline value, the smallest decrement was used. Such an analysis avoids the problem of carrying out multiple significance tests at different points in time and of specifying in advance the time at which the maximum effects will occur.

Results

The maximum individual increase in FEV₁, irrespective of when it occurred, was greater in both the fenoterol ($P < 0.05$) and ipratropium ($P < 0.05$) groups than in the placebo group, but no greater in the fenoterol than in the ipratropium group (Figure 1). Seventeen (65%) subjects in the fenoterol group and 10 (38%) in the ipratropium group ($\chi^2 = 3.78$, $P > 0.05$) had experienced their maximum bronchodilatation within 30 min or less after inhaling the drug.

The group mean increase in FEV₁ was greatest after 15 min in the fenoterol group (77 ml; $P < 0.01$ compared with baseline value), and after 60 min in the ipratropium group (103 ml; $P < 0.05$; Figure 2). The mean FEV₁ fell in the placebo group, the maximum reduction occurring after 30 min (80 ml; $P < 0.02$). One subject showed a fall in FEV₁ of 500 ml after inhaling placebo which was sustained throughout the observation period, but this accounted for only about a third of the reduction in the mean value.

The maximum individual increase in heart rate was significantly greater in the fenoterol group than in either the placebo group ($P < 0.01$) or the ipratropium group ($P < 0.001$), with no difference between the placebo and ipratropium groups (Figure 3). In the fenoterol group, the maximum increase in heart rate was greater than 30 beats min^{-1} in three (12%)

subjects, but less than 10 beats min^{-1} in half the subjects. The group mean heart rate increased significantly ($P < 0.001$) within 5 min of inhalation of fenoterol and the effect lasted throughout the 60 min observation period (Figure 4); in contrast, the mean heart rate declined in the placebo and ipratropium groups.

The maximum individual increase in needle

Figure 1 Maximum individual increase in FEV_1 (irrespective of time) after inhaling placebo (○), fenoterol 800 μg (●) or ipratropium 80 μg (■). Each point represents the value from one subject.

Figure 3 Maximum individual increase in heart rate (irrespective of time) after inhaling placebo (○), fenoterol 800 μg (●) or ipratropium 80 μg (■). Each point represents the value from one subject.

Figure 2 Increase in FEV_1 (mean $\pm$ 2 s.e. mean) after inhaling placebo (○), fenoterol 800 μg (●) or ipratropium 80 μg (■).

Figure 4 Increase in heart rate (mean $\pm$ 2 s.e. mean) after inhaling placebo (○), fenoterol 800 μg (●) or ipratropium 80 μg (■).

threading time was greater in the fenoterol group than in the placebo or ipratropium groups, but not significantly so ($P > 0.2$; Figure 5). Fenoterol appeared to prolong the group mean needle threading time shortly after it was inhaled (Figure 6), but the difference did not achieve statistical significance because of large fluctuations in each individual's needle threading ability.

The group mean needle threading time shortened significantly ($P < 0.01$) in the placebo and ipratropium groups (Figure 6).

In subjects who inhaled fenoterol, there were no correlations between the increase in FEV₁, the increase in heart rate and the development of tremor. The Pearson correlation coefficients for the changes at 5 min were -0.01 between FEV₁ and heart rate, -0.04 between FEV₁ and needle threading time, and 0.05 between heart rate and needle threading time. In one student, tremor was so marked that she was unable to thread the needle at all 45 min after inhaling fenoterol, but her heart rate had increased by only 3 beats min⁻¹.

Discussion

These results show that inhaled fenoterol and ipratropium both increase the FEV₁ significantly in normal subjects, suggesting that bronchodilation has occurred. This is in agreement with the results of Douglas *et al.* (1979) who showed that ipratropium increased expiratory flow by causing bronchodilation rather than by any other alteration in lung mechanics in 10 normal subjects. Systemic absorption of fenoterol was demonstrated in our trial by the increase in heart rate evident within 5 min of inhaling the drug. The rapid onset of this effect provides further evidence that a β_2 -adrenoceptor agonist drug given by metered dose inhaler can be absorbed from the lungs (Collier *et al.*, 1980), even though only about 10% of the dose administered reaches the lungs (Newman *et al.*, 1981b). As fenoterol is a β_2 -adrenoceptor agonist, the increase in heart rate is probably reflex and due to a reduction in peripheral resistance (Collier *et al.*, 1980); there was not enough time for subjects to measure blood pressure in our prac-

Figure 5 Maximum individual increase in needle threading time (irrespective of time) after inhaling placebo ($\circ$), fenoterol 800 μg ($\bullet$) or ipratropium 80 μg ($\blacksquare$). Each point represents the values from one subject. ∞ indicates one subject who failed to thread a needle.

Figure 6 Increase in needle threading time (mean) after inhaling placebo ($\circ$), fenoterol 800 μg ($\bullet$) or ipratropium 80 μg ($\blacksquare$). Confidence intervals were wider for the two active drugs than for placebo, and have been omitted from the figure for clarity.

tical class. Tremor is the dose-limiting effect of treatment with a β_2 -adrenoceptor agonist drug given by metered dose inhaler (Larsson & Svedmyr, 1977), and is caused by stimulation of β -adrenoceptors in skeletal muscle (Marsden *et al.*, 1967).

There appears to be no simple explanation for the reduction in FEV₁ in the placebo group. This practical class has been held on two subsequent years and similar results have been obtained, including the fall in FEV₁ in the placebo group. Sterling & Batten (1969) found that bronchoconstriction occurred in normal subjects who inhaled propellant, and the subjects in our placebo group had all practised with another placebo inhaler first; the other subjects had, too; but Sterling & Batten (1969) found that propellant-induced bronchoconstriction was regularly converted to bronchodilation by the addition of atropine or isoprenaline.

The lack of effect of inhaled ipratropium on heart rate in this trial may be due either to lack of systemic absorption of this quarternary ammonium compound, or to absence of cardiac vagal tone in these young subjects. However, in the lungs of these subjects ipratropium was an effective bronchodilator, suggesting that resting airway calibre is governed partly by parasympathetic tone in normal subjects.

The results show that the effects of inhaled fenoterol on heart rate and tremor vary considerably. While such variation may simply reflect differences in the amount of drug absorbed from the lungs, this is probably not the only explanation because there was no correlation between the effects on heart rate and tremor in individual subjects.

The students who participated in this study had previously taken a course in medical statistics which included the design and analysis of clinical trials. They were familiar with the concept of a confidence interval for a mean, and with its use in establishing whether the mean differed from zero at the 5% significance level based on a one-sample *t*-test. The changes observed in the placebo group provided a convincing demonstration of the danger of attributing changes after a drug has been given, to that drug in the absence of blinding and of a suitable control group. The students learned to recognise that it is necessary to carry out a two-sample test to compare the effect of an active drug with that of placebo, and of the problems of carrying out multiple significance tests when comparing the effects of three drugs at several points in time.

At the end of the practical class, the students were asked individually which drug they thought they had taken and why they thought so. The modes of action and unwanted effects of the two active drugs were then discussed by a pharmacologist and a chest physician.

The second year preclinical students taking part in this trial were naive subjects with no personal experience of bronchodilator drugs. In this practical class, they experienced the pharmacological effects of fenoterol and ipratropium and learned the importance of using a metered dose inhaler correctly. They were exposed to the practicalities of designing and carrying out a clinical trial, and the analysis of the data provided a useful test of their statistical skills.

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