# COMPARISON OF IPRATROPIUM BROMIDE AND FENOTEROL IN ASTHMA AND CHRONIC BRONCHITIS

Several single dose studies have indicated that the bronchodilator response to a cholinergic antagonist, e.g. atropine, ipratropium bromide, in patients with chronic bronchitis may be better than in asthmatic patients when compared with their response to a $\beta$-adrenoceptor agonist (Altounyan, 1964; Crompton, 1968; Petrie & Palmer, 1975; Chick & Jenne, 1977). The object of this study was to compare by dose-response curves the bronchodilator potency of ipratropium bromide and a $\beta$-adrenoceptor agonist, fenoterol, in two groups of patients, with asthma and with chronic bronchitis.

Six patients with asthma, aged 32–64 years, and six patients with clinical chronic bronchitis due to a history of moderate cigarette smoking, aged 50–72 years, were selected for this study. Their forced expiratory volume in one second ($FEV_1$) ranged between 25 and 75% of predicted normal (mean $\pm$ s.e. mean: $44.2 \pm 6.2\%$ for asthma group; $41.5 \pm 4.4\%$ for chronic bronchitis group). All patients had chronic, stable, partially reversible airways obstruction with greater than 15% $FEV_1$ increase after 200 µg salbutamol by pressurized aerosol. The patients were receiving maintenance treatment with combinations of prednisone, theophylline, disodium cromoglycate, beclomethasone diproprionate and salbutamol by pressurized aerosol.

The trials in both patient groups were randomized, balanced double-blind designs and conducted in the morning on three separate days. The treatments were 1) ipratropium bromide (Atrovent), 20 µg/inhalation, 2) fenoterol (Berotec), 200 µg/inhalation and 3) placebo, inactive propellant, all by pressurized aerosol. All aerosol canisters were prepared identical in appearance (Boehringer Ingelheim Pty. Ltd). It was necessary for there to be less than 15% variation between control, baseline $FEV_1$ values on the three trial days. All sympathomimetic and theophylline drugs were withdrawn for 12 h and 5 days respectively before each study day, but corticosteroids and disodium cromoglycate were continued at their maintenance doses. The written consent of each patient was obtained.

Resting, baseline $FEV_1$ readings (highest of three readings) with a Vitalograph and pulse rate were recorded. One treatment inhalation was then administered, and $FEV_1$ (best of two readings) and pulse rate measurements were repeated at 15 min intervals until no further $FEV_1$ improvement occurred. A second inhalation was given and the same procedure of $FEV_1$ and pulse rate recordings were taken. Thus, the cumulative doses were one, two, four, eight and sixteen inhalations of each drug and placebo. The results were submitted to statistical analysis using the paired Student's *t*-test.

There was no significant difference between the control $FEV_1$ values before the three treatments in the two patient groups. The mean peak % $FEV_1$ changes from control after all three treatments for the patients with asthma and chronic bronchitis are shown in Figures 1 and 2 respectively. The % $FEV_1$ increases from control after all drug doses were significantly greater than those after placebo ($P < 0.05$), except for one and two inhalations of ipratropium bromide in the asthma group and for four inhalations of fenoterol in the chronic bronchitis group. Fenoterol produced greater bronchodilatation than ipratropium bromide with all doses in the asthmatic patients, whereas in the patients with chronic bronchitis, the overall response to both drugs was similar, although significantly greater with ipratropium bromide after two and eight inhalations (see Figures 1 and 2). The mean peak pulse rate changes from control after all treatment doses are shown in Table 1. The pulse rate increase after sixteen inhalations of fenoterol was significantly greater than after placebo ($P < 0.05$) and ipratropium bromide ($P < 0.01$). No side-effects were reported by any patient.

**Table 1** The mean pulse rate changes from control (beats/min) for six patients with asthma and six patients with chronic bronchitis after cumulative doses of one, two, four, eight and sixteen inhalations of ipratropium bromide, fenoterol and placebo by pressurized aerosol.

| | *Number of inhalations* | | | | |
|---|---|---|---|---|---|
| *Drug* | *1* | *2* | *4* | *8* | *16* |
| | *Pulse rate change from control (beats/min)* | | | | |
| Ipratropium bromide | −0.3 | −0.8 | −3.8 | −5.3 | −5.7 |
| Fenoterol | +0.7 | −2.5 | −2.8 | −1.5 | +5.2 |
| Placebo | +0.3 | −0.2 | −1.8 | −3.3 | −2.8 |

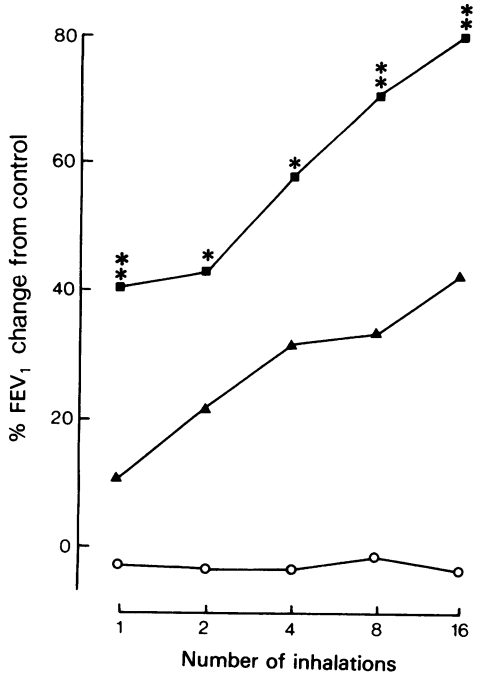


**Figure 1** The cumulative log dose (number of inhalations)/response (% $FEV_1$ change from control) curves for ipratropium bromide (▲), fenoterol (■) and placebo (O) by pressurized aerosol in six patients with asthma. (One inhalation of ipratropium bromide = 20 μg, of fenoterol = 200 μg.) Fenoterol > ipratropium bromide: ** $P<0.01$, * $P<0.05$.

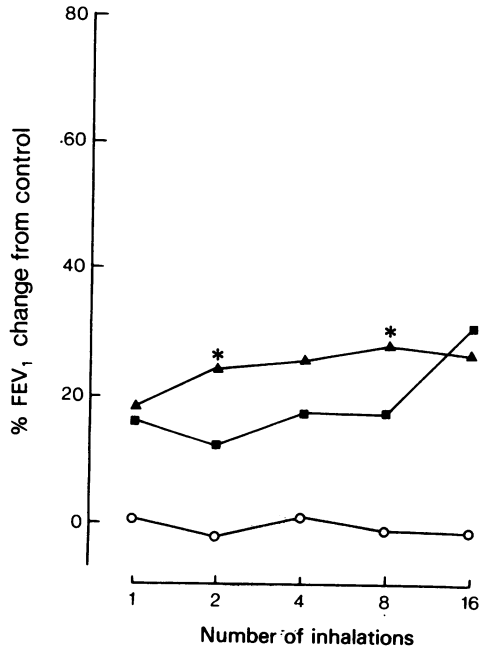


**Figure 2** The cumulative log dose (number of inhalations)/response (% $FEV_1$ change from control) curves for ipratropium bromide (▲), fenoterol (■) and placebo (O) by pressurized aerosol in six patients with chronic bronchitis. (One inhalation of ipratropium bromide = 20 μg, of fenoterol = 200 μg.) Ipratropium bromide > fenoterol: * $P<0.05$.

The molecular weights of the active bases of ipratropium bromide and fenoterol are 332 and 303 respectively. It was not possible to have the pressurized aerosols prepared to deliver equimolar doses by single inhalation. Thus, eleven times the equimolar dose of fenoterol compared with ipratropium bromide was used for each treatment. When the drugs were compared on an equimolar basis, ipratropium bromide was five times more potent than fenoterol in the asthmatic patients and sixteen times in the patients with chronic bronchitis. However, ipratropium bromide was much less effective as a bronchodilator than fenoterol in the asthmatic patients within the range of doses investigated, although in the patients with chronic bronchitis the drugs possessed similar efficacy. Patients with chronic bronchitis are known to possess bronchial hyperreactivity to both histamine and β-adrenoceptor agonists, although usually not to the same degree as asthmatic patients (Benson, 1978). In this study there was less reversible airways obstruction and less significant dose-responses in the patients with chronic bronchitis. The enhanced response to ipratropium bromide compared with fenoterol in these patients suggests increased cholinergic tone in bronchial smooth muscle. Ipratropium bromide has been shown in chronic bronchitis not to affect sputum volume, viscosity or mucociliary clearance (Matthys, Muller, Konietzo & Adam, 1975; May & Palmer, 1977; Ruffin, Wolff, Dolovich, Rossman, Fitzgerald & Newhouse, 1978). Considering the heart rate effects, both drugs demonstrated a wide margin of safety. In conclusion, this study suggests that ipratropium bromide may be a valuable bronchodilator in patients with chronic bronchitis. Larger doses of ipratropium bromide require investigation with respect to efficacy and toxicity.

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## MEASUREMENT OF SYSTOLIC TIME INTERVALS

In recent years, the use of the measurement of systolic time intervals (STI) as a measure of cardiac contractility has become increasingly more popular (Dobbs, Kenyon & Dobbs, 1977; Lewis, Milne & Goldberg, 1976; Sykes, Wright, Malins & Pentecost, 1977). Briefly, the technique involves the simultaneous recording of electrocardiogram, phonocardiogram, and the carotid artery pressure pulse, from which the time of total electromechanical systole (QS2) and left ventricular ejection time (LVET) can be obtained. The pre-ejection period (PEP) and various derived quantities e.g. PEP/LVET, can be calculated. The most commonly used protocol involves the subject resting in a supine position for between 10–30 min followed by the recording of between ten and twenty consecutive heart beats. The mean values for LVET, QS2 and heart rate are then calculated, and the LVET and QS2 data are corrected using the regression equations obtained by Weissler, Harris & Schoenfeld (1968),

$$\textit{viz} \quad \left.\begin{aligned} \text{LVET} &= -1.7\,\text{HR} + 413 \\ \text{QS2} &= -2.1\,\text{HR} + 546 \end{aligned}\right\} \text{ males}$$

The data leading to these regression equations were obtained from a large number of normal male subjects (similar data were obtained from female subjects) with the recordings being made between 08.00 and 10.00 h, although the latter time could be extended to 15.00 h. This technique has been applied to investigations into the pharmacodynamic effects of digoxin and beta methyl digoxin in man (Das, Talmers & Weissler, 1977; Hinderling & Garrett, 1977) where the shortening of QS2 or LVET has been used as a measure of the cardiac effects of these drugs. However, there have been few studies carried out in which changes in STI following placebo administration have been measured.

In a balanced cross-over experiment undertaken in this laboratory, to investigate such effects, four healthy, male volunteer subjects, aged between 20 and 35 years were used. Each gave his informed consent, and the experiment was approved by the Hospital Research and Ethical Committee. The subjects were given a standardized, light breakfast at 07.00 h on each morning of the experiment, but this did not include tea or coffee. A light lunch, including 500 ml fluid was given after the 6 h recordings had been made. Systolic time intervals were measured following the i.v. administration of digoxin (1 mg), $\beta$-methyl digoxin (1 mg), ouabain (0.5 mg) and a placebo consisting of propylene glycol which was used as the vehicle for the other injections. The injections were carried out at 08.30 h and systolic time intervals were measured at 30 min intervals up to 6 h following injection, and then hourly up to 12 h. Recordings of twenty consecutive beats were made in the supine

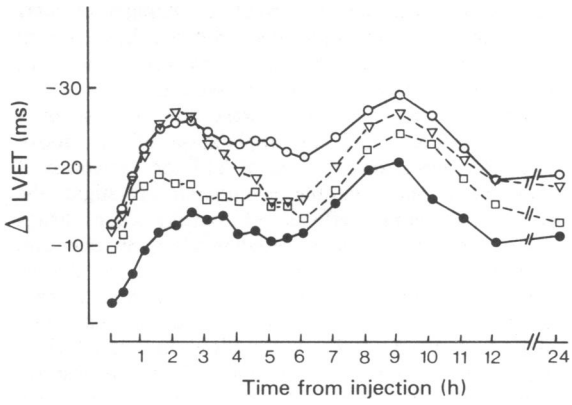


**Figure 1** Changes in LVET obtained from one subject after placebo (●), digoxin (○), $\beta$-methyl digoxin (▽) and ouabain (□). The mean s.d. for each point is ± 5.0 ms.