

Single dosing comparison of the relative cardiac β_1/β_2 activity of inhaled fenoterol and salbutamol in normal subjects

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Abstract

Background—The aim of the present study was to compare the dose related effects of fenoterol and salbutamol on cardiac β_1 and β_2 receptors using the β_1 selective antagonist atenolol, in order to dissect out relative β_1/β_2 mediated responses.

Methods—Fourteen normal volunteers were randomised to receive pretreatment with either atenolol 25 mg or placebo, followed by inhaled fenoterol or salbutamol in equal doses by weight (cumulative doses of 1 mg and 4 mg). Measurements were made 30 minutes after inhaling each dose of β_2 agonist. Values (mean and 95% CI) were expressed as a change from baseline.

Results—At 4 mg fenoterol produced equivalent falls in serum potassium and increases in tremor to salbutamol. The mean (95% CI) increase in heart rate (beats/min) with fenoterol at 4 mg after placebo was 47 (41–53) and after atenolol was 34 (28–40), with values for salbutamol being 46 (40–52) after placebo and 30 (24–36) after atenolol. The inotropic response (stroke distance) after atenolol at the 4 mg dose was 5.0 (3.9–6.1) cm for fenoterol and 4.7 (3.5–5.9) cm for salbutamol. There were no significant differences in heart rate or stroke distance response between the two drugs after either placebo or atenolol. Furthermore, ECG effects (Q-Tc and T wave) of fenoterol and salbutamol were comparable at both doses.

Conclusions—These results show that there is no difference in the respective chronotropic or inotropic activities of fenoterol and salbutamol on cardiac β_1 or β_2 receptors when given at higher than conventional doses.

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In recent case control studies from New Zealand it has been suggested that the use of inhaled fenoterol may be associated with an increased risk of death in acute severe asthma. There is conflicting evidence as to whether higher doses of inhaled fenoterol produce greater cardiac effects than salbutamol in both normal volunteers and in patients

with asthma.^{1–3} These studies have not, however, determined whether dose related cardiac effects are mediated by stimulation of β_1 or β_2 adrenoceptors. The aim of the present study was therefore to compare dose related effects of inhaled fenoterol and salbutamol on cardiac β_1 and β_2 receptors, using the selective β_1 antagonist atenolol to dissect out relative β_1/β_2 mediated responses. The doses were chosen to compare the two drugs on a weight-for-weight basis, since fenoterol has recently been reformulated, like salbutamol, to deliver 100 μg per puff. If the hypothesis that fenoterol stimulates cardiac β_1 adrenoceptors to a greater degree than salbutamol was correct, then it might be expected that atenolol would blunt the chronotropic (heart rate) and inotropic (contractile) effects of fenoterol more than salbutamol.

Methods

STUDY DESIGN

Fourteen healthy subjects (eight men, mean (SE) age 24(1) years) were randomised into a double blind, placebo controlled crossover study. On an initial visit all volunteers underwent a standardised exercise step test 60 minutes after prior oral dosing with placebo, and then again 150 minutes after receiving atenolol 25 mg in order to evaluate the degree of β_1 blockade. Subjects then attended the laboratory, having fasted overnight, on four occasions separated by at least three days. Each subject was given either oral atenolol 25 mg or placebo, and 150 minutes after tablet ingestion baseline measurements of heart rate, serum potassium, finger tremor, systolic blood pressure, diastolic blood pressure, stroke distance (a measure of inotropicity), electrocardiographic parameters (T wave, Q-Tc) and plasma atenolol levels were undertaken. Subjects then inhaled a cumulative dose of 1 mg (five puffs of 200 μg per actuation) and 4 mg (a further 15 puffs of 200 μg per actuation) of either fenoterol or salbutamol via a metered dose inhaler, the doses being separated by 40 minutes. Measurements (excluding atenolol levels) were repeated 30 minutes after inhaling each dose. Blood samples for plasma fenoterol and salbutamol concentrations were taken at 5, 15, and 30 minutes after the 1 mg dose, and at 5, 15, 30, and 60 minutes after the 4 mg dose.

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MEASUREMENTS

Serum potassium level was measured by flame photometry, plasma atenolol level by high performance liquid chromatography, plasma salbutamol level by capillary gas chromatography, and plasma fenoterol level by radioimmunoassay. An electrocardiogram was recorded on standard lead II for measurement of heart rate, Q-T (and hence Q-Tc) interval and T wave amplitude. Systolic and diastolic blood pressures were recorded by a semiautomatic sphygmomanometer. Finger tremor was measured by a previously

validated method with an accelerometer transducer. Stroke distance was measured non-invasively from the ascending aorta using a 1.9 MHz continuous wave non-imaging transducer (Hewlett-Packard System 77020A). Stroke distance (cm) is the linear analogue of stroke volume (cm^3), as the cross sectional area of the aortic root is constant.

STATISTICAL ANALYSIS

With heart rate as the primary end point, the use of 14 subjects was sufficient to detect a difference in heart rate of 10 beats/min between treatments with 94% power ($\beta = 0.06$) at the 95% level ($\alpha = 0.05$, two tailed). Comparisons between treatments were made by multifactorial analysis of variance. Values are shown as means and 95% confidence intervals (CI).

Results

Mean baseline values for all responses measured were not significantly different between study days. A highly significant ($p < 0.001$) dose-response effect occurred between 1 mg and 4 mg for all measured responses. After prior dosing with placebo or atenolol the peak exercise heart rates (beats/min) were 163 (158–168) and 131 (126–136) respectively, a mean reduction in peak exercise heart rate of 21% (20–22%). Atenolol levels (ng/ml) before the exercise test and inhaling fenoterol or salbutamol were not significantly different being 189 (171–207), 159 (139–179), and 186 (167–205) respectively. Plasma fenoterol concentrations were lower than those of salbutamol but a dose related fourfold increase occurred for both drugs. Peak levels occurred at five minutes after inhalation for both fenoterol and salbutamol (fig 1A).

CARDIOVASCULAR AND ECG RESPONSES

At the 4 mg dose fenoterol produced an increase in heart rate (beats/min) of 47 (41–53) after placebo, with atenolol significantly blunting this effect to 34 (28–40), $p < 0.01$. A comparable chronotropic response was seen with salbutamol after placebo of 46 (40–52), with atenolol significantly reducing this response to 30 (24–26), $p < 0.001$ (fig 1B). The percentage blunting of heart rate responses produced by atenolol at the 4 mg dose was 14% (6–22%) for fenoterol and 16% (8–24%) for salbutamol. At the 4 mg dose, after atenolol, the increase in stroke distance (cm) with fenoterol was 5.0 (3.9–6.1) and for salbutamol was 4.7 (3.5–5.9) (fig 1B). There were no significant differences in heart rate or inotropic response between the two drugs after either placebo or atenolol. The increase in systolic blood pressure (mm Hg) after placebo was greater ($p < 0.05$) for fenoterol than for salbutamol: 16 (14–18) v 11 (8–14). The percentage reduction in systolic blood pressure produced by atenolol at the 4 mg dose was comparable for the two drugs (fenoterol v salbutamol): 10% (6–14%) v 8% (4–12%). The fall in diastolic blood pressure (mm Hg) was not significantly different between fenoterol and

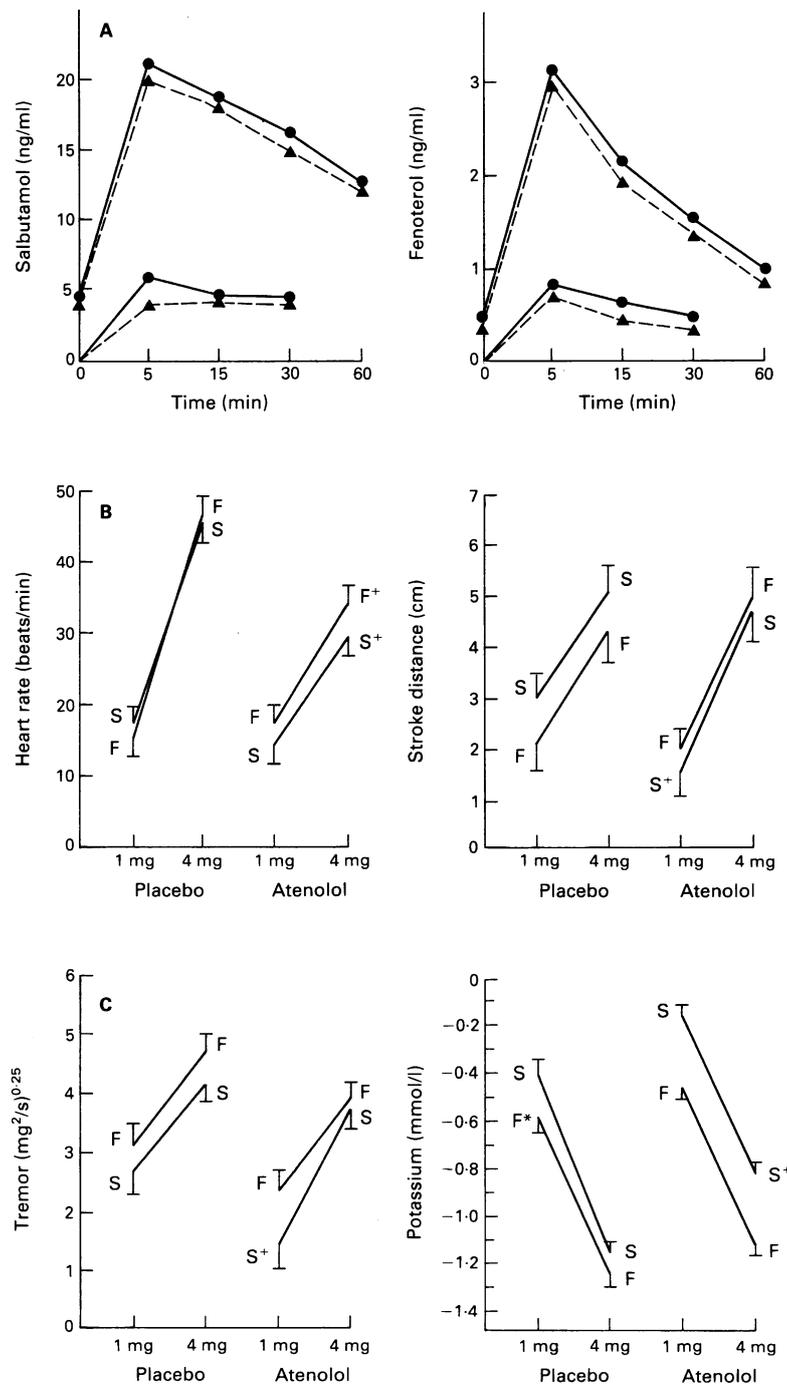


Figure 1 (A) Mean plasma levels (ng/ml) of salbutamol and fenoterol at 5, 15, and 30 minutes after inhalation of 1 mg and 5, 15, 30, and 60 minutes after inhalation of 4 mg following pretreatment with placebo (triangles) or atenolol 25 mg (circles). (B) Mean (SE) responses for heart rate and stroke distance in response to fenoterol (F) and salbutamol (S), 1 mg and 4 mg, as a change from baseline following pretreatment with placebo and atenolol 25 mg, and (C) mean (SE) responses for tremor and levels of potassium. *Significant difference between responses to F and S after placebo; + significant difference in responses to F, S, or both after atenolol v placebo.

salbutamol at either dose. At 1 mg and 4 mg there were no significant differences between fenoterol and salbutamol for T wave flattening or Q-Tc prolongation after either placebo or atenolol. At the 4 mg dose values after placebo for fenoterol and salbutamol respectively were, Q-Tc (s): 0.41 (0.39-0.43) v 0.41 (0.39-0.43) and T wave amplitude (mV): 0.15 (0.11-0.19) v 0.16 (0.11-0.21).

POTASSIUM AND FINGER TREMOR RESPONSES

Fenoterol produced a fall in serum potassium of 0.59 (0.49-0.69) mmol/l after the 1 mg dose and 1.26 (1.17-1.35) mmol/l after the 4 mg dose. The values for salbutamol were: 0.39 (0.29-0.49) mmol/l after 1 mg and 1.15 (1.07-1.23) mmol/l after 4 mg (fig 1C). The fall in potassium was significantly greater for fenoterol than salbutamol only at the 1 mg dose ($p < 0.05$). Finger tremor responses ($\text{mg}^2/\text{s}^{0.25}$) to fenoterol were: 3.2 (2.5-3.9) at 1 mg and 4.7 (4.2-5.2) at 4 mg, and there were no significant differences in comparison with salbutamol: 2.6 (2.0-3.2) and 4.1 (3.6-4.7) (fig 1C).

Discussion

The results of this study showed that there were no significant differences in the chronotropic (heart rate) or inotropic (stroke distance) responses to fenoterol and salbutamol either at 1 mg or 4 mg doses, even after treatment with atenolol. Since atenolol, a selective β_1 adrenoceptor antagonist, produced equivalent effects on these responses, this infers that fenoterol and salbutamol have equal activity at cardiac β_1 and β_2 adrenoceptors. It was initially thought that cardiac β_1 adrenoceptors consisted solely of the β_1 subtype. It is now clear, however, that both cardiac β_1 and β_2 adrenoceptors exist⁴ and that cardiac β_2 adrenoceptors are responsible for mediating both chronotropic^{5,6} and inotropic⁷ responses in vivo.

Our study is the first to compare inotropic effects of inhaled fenoterol and salbutamol using stroke distance, as opposed to previous studies which have used indirect parameters such as systolic time intervals.^{1,3} In this study the response in stroke distance was not different between treatments at doses of 1 mg or 4 mg, and was not significantly blunted by atenolol except at the 1 mg dose for salbutamol. In vitro studies with selective β_1 and β_2 antagonists in human myocardium have shown that the inotropic effect of fenoterol is mediated predominantly by β_2 adrenoceptors, even at high concentrations.⁸ Furthermore, fenoterol acts as a full agonist and is more potent than salbutamol, which is a partial agonist, on cardiac β_2 receptors.⁸ It might therefore have been expected that fenoterol would cause greater cardiac β_2 effects in our study, but this was clearly not the case. This highlights differences between in vitro and in vivo effects of β_2 agonists on cardiac β adrenoceptors. For example, in a comparison between isoprenaline and salbutamol⁹ no differences were found for dose-response effects on heart rate and Q-Tc, which would not

have been expected from in vitro data.

It was also found that atenolol partially blunted known β_2 responses such as hypokalaemia and tremor. This was to be expected since it is known that, although atenolol is β_1 selective, it is not β_1 specific as an antagonist. In this respect previous studies have shown that atenolol causes dose related β_2 blockade.⁶ It was not surprising, therefore, to find in our study that atenolol also partially blunted the chronotropic response which is mediated by β_2 adrenoceptors.^{5,6}

There are conflicting data from the literature on the relative cardiac effects of fenoterol and salbutamol. Indeed, two studies from the same laboratory comparing equal doses by weight showed that fenoterol caused greater chronotropic and systolic blood pressure responses in normal volunteers,¹ whereas in asthmatic patients no differences were found.³ Crane and coworkers¹ may have found different results in comparison with the present study since measurements of systemic responses were carried out at five and 15 minutes after each dose, whereas in our study chronotropic and inotropic responses were measured at 30 minutes after the dose. It is conceivable that peak effects of fenoterol but not salbutamol may have occurred within 15 minutes, resulting in an apparent difference between the two drugs. Wong and coworkers,² comparing fenoterol 200 μg per puff and salbutamol 100 μg per puff, not surprisingly showed greater effects on a number of β_2 mediated responses including heart rate, tremor, and potassium. Unlike the present study, none of the above studies attempted to dissect out relative effects on cardiac β_1/β_2 receptors.

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