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A comparison of the effect of salmeterol and salbutamol in normal subjects

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1 The effects of salmeterol hydroxynaphthoate (50 μg, 8.3×10^{-8} M) and salbutamol (200 μg, 3.5×10^{-7} M) on sGaw were compared in a double-blind, placebo-controlled, randomised study in 10 normal subjects.
2 SGaw increased by 29% (14–43) (mean (CI)), 5 min after salmeterol and by 35% (19–51) at 15 min compared with an increase of 32% (14–51) and 37% (10–63) after salbutamol and 4% (−3–11) and 8% (0–16) after placebo.
3 The mean area under the sGaw-time curve (AUC_{480}) after salmeterol inhalation was 22500 kPa^{-1} (10100–39500) compared with 14100 kPa^{-1} (8020–24500) after salbutamol and 5300 kPa^{-1} (1500-10400) after placebo.
4 Salmeterol produced a significantly prolonged bronchodilator effect compared with salbutamol in normals.

Keywords salmeterol hydroxynaphthoate salbutamol bronchodilator

Introduction

β-adrenoceptors are widely distributed in human airways (Carstairs *et al.*, 1985). Inhaled selective β_2-adrenoceptor agonists are the most effective and most widely used bronchodilator drugs in asthma therapy.

Salmeterol hydroxynaphthoate is a new long acting selective β_2-adrenoceptor agonist. When compared with salbutamol an equi-effective dose has been shown to produce significantly longer bronchodilatation in asthmatics (Boyd *et al.*, 1990; Ullman & Svedmyr, 1988). In a placebo controlled comparison with salbutamol, salmeterol protected against histamine induced bronchoconstriction for 12 h, significantly longer than for salbutamol (Campus-Gongora *et al.*, 1990). Similar results were found in protection against methacholine induced bronchoconstriction (Breach *et al* ., 1990). In a placebo controlled comparison in prevention of exercise induced asthma, salmeterol was effective for up to 12 h after administration whereas the effect of salbutamol had worn off after 6 h (Newham *et al.*, 1990). Clinical evidence of the importance of the prolonged duration of action of salmeterol is shown by benefit in patients with nocturnal asthma (Fitzpatrick, 1990; Ullman *et al.*, 1990).

Inhaled β_2-adrenoceptor agonists cause bronchodilatation in normal subjects as well as in patients with airflow obstruction. Specific airways conductance (sGaw) is a sensitive test of airway calibre allowing small changes in normals and asthmatics to be detected in the absence of changes in more conventional tests such as FEV_1 (Skinner & Palmer, 1974). Dose-response curves in normal subjects to inhaled β-adrenoceptor agonists have been constructed showing an increase of 30–70% in sGaw after salbutamol (Gribbin *et al.*, 1979).

It is difficult to examine drug effect and duration in patients with severe asthma because of concomitant therapy and inherent variability in airway calibre. In asthmatics the duration of bronchodilator action represents the summation of the relaxant effect on the airways and the antagonistic constrictor mechanisms. In studying β-adrenoceptor mechanisms duration of drug action may be better assessed in normal subjects where no constrictor mechanisms occur. The aim of this study was to compare the duration of action of salmeterol with that of salbutamol on normal human airways in a controlled double placebo, double-blind manner.

Methods

Subjects

Ten normal volunteers, six males and four females (Table 1) were studied. Two subjects were atopic as judged by positive skin tests to common allergens but

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Table 1 Subject characteristics

Subject	Age (years)	Sex	Atopy	AUC_{480} sGaw (kPa^{-1}) Salmeterol	Salbutamol	Placebo
1	41	M	+	10100	9840	3840
2	31	M	−	21800	14800	6970
3	30	M	−	7400	1560	4320
4	28	M	−	62100	26500	7380
5	27	F	−	36200	23300	17700
6	30	F	+	17000	15300	6900
7	32	M	−	27100	13200	−3420
8	25	F	−	11700	14700	6540
9	31	F	−	6180	2880	−78
10	31	M	−	25300	19000	2898

AUC_{480} sGaw represents area under the curve of specific airways conductance (sGaw) *vs* time (min) over 8 h.

none had any current symptoms. No subject had any past history of asthma nor any recent respiratory infection. No subject was taking regular medication. All subjects gave written informed consent for the study which was approved by the hospital Ethics committee.

Study design

Subjects were studied in a double-blind randomised manner on three separate days. On each occasion sGaw was determined using a constant volume computerised body plethysmograph (Chowienczyk *et al.*, 1981). Each measurement was taken as the mean of six readings. Two baseline measurements were made 5 and 3 min prior to drug administration. Subjects received salbutamol (200 μg), salmeterol (50 μg) or double placebo from matched metered dose inhalers. SGaw was then repeated at 5, 15, 30, 60 min and 2, 3, 4, 5, 6, 7 and 8 h.

Data analysis

SGaw was expressed as mean and 95% confidence intervals (CI). Baseline sGaw on the 3 separate days was compared by analysis of variance (ANOVA). SGaw after drug administration was compared by analysis of variance of repeated measures with Wilcoxon's rank sum test applied at selected times. The area under the curve (AUC_{480}) of sGaw *vs* time for each subject and each drug was calculated (s^{-1} kPa^{-1} × min × 60) and Wilcoxon's rank sum test applied.

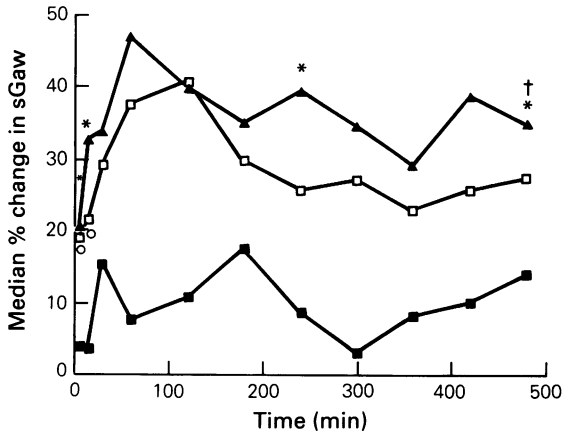

Figure 1 Median % change in sGaw after salmeterol (▲), salbutamol (□) and placebo (■). Cross shows significant differences between salmeterol and salbutamol; (†) $P < 0.05$. Asterisks show significant differences between salmeterol and placebo; (*) $P < 0.05$. Small open circles show differences between salbutamol and placebo; (○) $P < 0.05$.

Results

Tremor was reported in two subjects after salmeterol inhalation but no other adverse effects were noted.

Mean baseline sGaw did not differ significantly between the three study days. SGaw values were 1.56 s^{-1} kPa^{-1} (1.31–1.81) (mean (CI)) for salmeterol, 1.51 s^{-1} kPa^{-1} (1.24–1.77) for salbutamol and 1.66 s^{-1} kPa^{-1} (1.29–2.02) for placebo. At 5 min after drug inhalation sGaw did not differ significantly on any of the 3 treatment days. However, there was a significant difference between salmeterol and placebo for the % change in sGaw (Figure 1). At 15 min sGaw after salmeterol was 2.09 s^{-1} kPa^{-1} (1.73–2.45) compared with 2.09 s^{-1} kPa^{-1} (1.64–2.49) after salbutamol and 1.75 s^{-1} kPa^{-1} (1.40–2.13) after placebo. There was a significant difference between salbutamol and placebo ($P < 0.05$), but salmeterol did not differ significantly from salbutamol or placebo. However, the percent change in sGaw after salmeterol was significantly greater than after placebo ($P < 0.01$) as it was after salbutamol compared with placebo ($P < 0.05$). At 4 h sGaw after salmeterol and salbutamol was significantly greater than after placebo ($P < 0.01$) but did not differ between treatments. However at 8 h sGaw after salmeterol was greater than after salbutamol ($P < 0.05$). SGaw after salbutamol did not differ significantly from that after placebo (Figure 1). There was considerable intersubject variation in baseline sGaw and in the magnitude of individual response to β_2-adrenoceptor agonists.

As assessed by AUC, salmeterol produced a significantly greater duration of bronchodilatation than salbutamol ($P < 0.05$) and placebo ($P < 0.01$). Salbutamol had a significantly greater effect than placebo ($P < 0.01$). Mean area under the curve (AUC) for absolute sGaw over 8 h after salmeterol was 22500 kPa^{-1} (10100–39500) compared with 14100 kPa^{-1} (8020–24500) after salbutamol and 5300 kPa^{-1} (1480–10400) after placebo (Table 1).

Maximum sGaw after salmeterol was 2.65 s^{-1} kPa^{-1}

(2.14–3.28) compared with 2.38 s^{-1} kPa^{-1} (1.94–2.83) after salbutamol. This represents a mean maximal increase of 76% after salmeterol and 59% after salbutamol which was significantly different ($P < 0.05$).

Discussion

This study is the first to illustrate the prolonged duration of bronchodilator action of a single dose of inhaled salmeterol (50 μg) compared with salbutamol (200 μg) in normal subjects. Area under the curve of sGaw against time was significantly greater for salmeterol compared with salbutamol which differed significantly from placebo.

The AUC_{480} results illustrate a significantly prolonged bronchodilator response to salmeterol compared with salbutamol. Our results are consistent with those in asthmatics (Boyd *et al.*, 1990; Sandstrom *et al.*, 1989; Ullman & Svedmyr, 1988). In healthy subjects salmeterol protected subjects from the effect of inhaled histamine for 12 h whereas salbutamol showed a protective effect at 1 h only (Maconochie, 1988). In asthmatics salmeterol protected for longer than salbutamol against bronchoconstriction induced by histamine, methacholine and exercise (Breach *et al.*, 1990; Campus-Gongora *et al.*, 1990; Newham *et al.*, 1990). In conscious guinea-pigs salmeterol inhibited histamine induced bronchoconstriction for over 7 h compared with 1.5 h for salbutamol. In anaesthetised cats the bronchodilator effect of inhaled salmeterol and salbutamol was comparable but the duration of action was doubled for salmeterol. The relaxant activity of salmeterol on human bronchial smooth muscle *in vitro* was twice that of salbutamol (Johnson, 1990).

Standard doses of two puffs of salmeterol (50 μg) and salbutamol (200 μg) were compared in this study as in many others (Johnson, 1990). The mean maximal effect was slightly greater after salmeterol compared with salbutamol but this was often delayed. We cannot exclude that greater efficacy may have contributed to the prolonged bronchodilator effect that we observed. If maximal bronchodilatation was achieved in some or all of our subjects then sGaw may effectively have been truncated. This would not affect our conclusions regarding the prolonged duration of action of salmeterol compared with salbutamol at these doses. The dose of salmeterol was a quarter less than that of salbutamol on a molar basis and it has been suggested that it is 4–6 fold more potent *in vitro* as a β-adrenoceptor agonist (Johnson, 1990). The mechanism of the prolonged duration of action of salmeterol compared with other β-adrenoceptor agonists in general is unknown but may be due to the large non-polar *N*-substituent binding firmly to an adjacent ('exo receptor') region of the cell membrane (Johnson, 1990).

There is some evidence that the onset of bronchodilator action of salmeterol is slower than that of salbutamol. This was found in some patients with asthma (Boyd *et al.*, 1990), in reversal of methacholine induced bronchoconstriction (Breach *et al.*, 1990), and *in vitro* in guinea pig trachea (Johnson, 1990). However, we found no significant difference in change of sGaw for 15 min after salmeterol compared with salbutamol. This may be due to the increased calibre of airways in normals compared with asthmatics but one study in asthma also found no difference between these drugs as regards onset of action (Ullman & Svedmyr, 1988).

We have demonstrated the prolonged duration of action of salmeterol compared with salbutamol in normal human airways. Studies in normal airways, in the absence of constrictor mechanisms may lead to valuable information concerning duration of bronchodilator drug action.

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