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Speeds of Action of Single Doses of Formoterol and Salbutamol Compared with Placebo in Reversing Methacholine-induced Bronchoconstriction

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SUMMARY: We compared the speeds of action of two doses of the long acting β-agonist formoterol (12 μg and 24 μg) with those of salbutamol (400 μg) and placebo using a double-blind, randomized, cross-over study design in 16 asthmatic subjects. A methacholine test was used on four separate study days to produce a standardized degree of bronchoconstriction (a decrement in FEV1 $\geq$20%) and one of the study medications as dry powder was administered immediately afterwards via an Aerolizer™ inhaler device. The speeds of recovery were estimated from measurements of FEV1 over the following 2–90 min. All active treatments produced significantly greater bronchodilation than placebo as early as 2 min after administration, and their peak effects within 10 min; and no significant differences were noted between them. Mean recovery times by 50% of the FEV1 decrement provoked by methacholine were significantly shorter for the active medications: 5.7 min (formoterol 24 μg), 6.4 min (salbutamol 400 μg), 10.2 min (formoterol 12 μg), and 53.1 min (placebo); the respective times for recovery by 80% being 18.0, 17.4, 22.1, and 83.3 min. We conclude that single doses of the dry powder formulations of all three active treatments produce rapid and effective bronchodilation. This conclusion should not, however, be extrapolated to the regular use of these medications, since differential down-regulation and tachyphylaxis may then exert an influence.

KEY WORDS: Speed of bronchodilator action, Formoterol, Methacholine-induced bronchoconstriction.

INTRODUCTION

Inhaled β_2-agonists are widely used in the treatment of asthma both as regular prophylaxis and as rescue medication for the relief of acute symptoms. For prophylaxis newly developed long acting β_2-agonists, such as salmeterol and formoterol, have provided a useful therapeutic advance because they need to be administered only twice daily. This prolonged action may, however, make them less suitable as rescue medication, since an urgent need for bronchodilatation might encourage overdosing in the affected individual. Furthermore, salmeterol has been shown to have a slower onset of action than short acting β_2-agonists such as salbutamol and terbutaline.[1–3] This potential disadvantage has not been evident from initial studies of formoterol when administered by metered dose inhaler.[4–9]

Studying the effect of bronchodilators on spontaneously occurring bronchoconstriction in a controlled way is difficult, and so we have used an experimental model of bronchoconstriction (a standardized methacholine provocation test) as a tool for investigations of this nature.[3] Thus clear differences were demonstrable between salmeterol and salbutamol in their speeds of action when used at the doses prescribed in clinical practice. We have now compared two doses of formoterol (12 μg and 24 μg) with salbutamol (400 μg) and placebo using the same methods, but as dry powders. Our aim was to assess the speed of action of formoterol, and we studied dry powder formulations because chlorofluorocarbon propellants will soon be unavailable for β_2-agonist delivery from metered dose inhalers. Since bioavailability appears to be less for dry powder formulations than for metered dose inhalers, we did not similarly assess the effects of formoterol 6 μg or salbutamol 200 μg.

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METHODS

Subjects

Asthmatic subjects aged 18–70 years of either sex were recruited from the population of a hospital based Asthma Clinic until 16 completed the investigation. This number would provide an 80% chance of detecting a 10% difference in the effects of the study medications on FEV1 at the 5% level of significance. A lesser difference was considered to be of little clinical importance. All participants gave written informed consent and the investigation was approved by the local ethical committee. All had asthma requiring treatment with bronchodilators and all had quantifiable levels of airway responsiveness, with a PD20 (provoking dose of methacholine responsible for a 20% decrement in FEV1) of less than 3200 μg.[10] All were able to use the medication delivery device effectively.

Subjects who had an exacerbation of their asthma, had any change in their medication, or had been exposed unusually to a known relevant allergen within the preceding month or during the course of the study were excluded. Further exclusion criteria debarred subjects with an FEV1 <60% predicted or <1.5 l immediately before any of the methacholine tests; subjects with a history of myocardial infarction, cardiac arrhythmias or other serious intercurrent disease; and women who were pregnant or lactating, or who were of child bearing potential without adequate means of contraception.

Short acting inhaled β-agonists were withheld for 8 h before each methacholine test, and inhaled anticholinergic drugs, oral β-agonists, theophyllines, and antihistamines for 24 h before each test. Regularly used inhaled corticosteroids were taken at their usual time on each study day. No subject had been using β blocking agents or long acting β-agonists.

Study protocol

The investigation was carried out using a randomized, double-blind, cross-over design. Each subject underwent a methacholine test on 4 separate days, at the same time of day ($\pm$1 h), at intervals of at least 2 days, over a period up to 28 days. Immediately after each test, when the decrement in FEV1 was $\geq$20%, each subject received one of the four study medications: formoterol 12 μg (f12), formoterol 24 μg (f24), salbutamol 400 μg (s), or placebo (p). Each was given as a dry powder from an Aerolizer™ inhaler device (Italseber Farmaceutica, Italy). Subjects were allocated in equal numbers at random to receive medication in one of four medication sequences: p:s:f12:f24, f24:f12:s:p, s:f24:p:f12, f12:p:f24:s.

Upon arrival on each study day, the baseline FEV1 was recorded. For study days 2–4 baseline FEV1 was required to be within 15% of that measured on the first study day. If it was outside this range, the subject was asked to return on a later day. Methacholine was administered by aerosolized solution from a dosimeter in sequential doubling cumulative doses from 3.125 μg to 6400 μg at 5 min intervals until FEV1 decreased by at least 20%, according to our usual protocol.[10] The study medication was then given immediately. FEV1, as the mean of three technically satisfactory measurements, was recorded thereafter at 2 min intervals for 10 min, and then at 5 min intervals for a further 80 min. To avoid unnecessary discomfort from exhaling to residual volume, each manoeuvre was terminated shortly after 1 s as signalled by an electronic bleep. Any subject who had not recovered fully to the baseline level of FEV1 at the end of the 90 min surveillance period was given additional bronchodilator medication as appropriate. PD20 was derived by linear interpolation.

Statistical analysis

Analysis of covariance was used initially to compare FEV1 recoveries following the various study medications, allowing for baseline FEV1, log PD20, and lowest FEV1, but these covariates reduced between subject variation only, not within subject variation. As a consequence they did not help explain differences between study days for individual subjects, and so analyses of variance rather than covariance were used in the final analyses.

Speed of bronchodilator action was assessed primarily by the times required to recover by 50% and by 80% from the decrement in FEV1 caused by the administration of methacholine. Whenever FEV1 had not recovered by such degree during the 90 min surveillance period, a recovery time of 95 min was assigned arbitrarily.

Primary analyses of variance were used to assess whether there were any differences between the study medications in 50% recovery time, 80% recovery time, maximum FEV1 attained, and time to reach this maximum. When this was found to be so, two subsidiary series of analyses were carried out. Firstly, placebo was compared with the mean of the three active treatments, and the placebo–bronchodilator effect demonstrated by this was taken into account in comparing salbutamol 400 μg with formoterol 24 μg. Secondly, the two formoterol treatments were compared after allowing for any placebo–bronchodilator effect.

RESULTS

The mean age of the 16 subjects completing the study was 38.4 years, and nine were female. They had asthma

Table 1 Mean baseline FEV1, mean lowest FEV1, and geometric mean PD20 before each study medication (with 95% confidence intervals).

	Placebo	Salbutamol 400 μg	Formoterol 12 μg	Formoterol 24 μg
Baseline FEV1 (l)	2.84 (2.39–3.29)	2.85 (2.40–3.31)	2.79 (2.34–3.23)	2.86 (2.41–3.32)
Lowest FEV1 (l)	2.14 (1.78–2.50)	2.09 (1.73–2.45)	2.09 (1.71–2.47)	2.07 (1.74–2.39)
PD20 (μg methacholine)	63.8 (25.3–161.1)	64.3 (29.1–141.9)	61.0 (22.8–163.3)	66.4 (29.0–152.1)

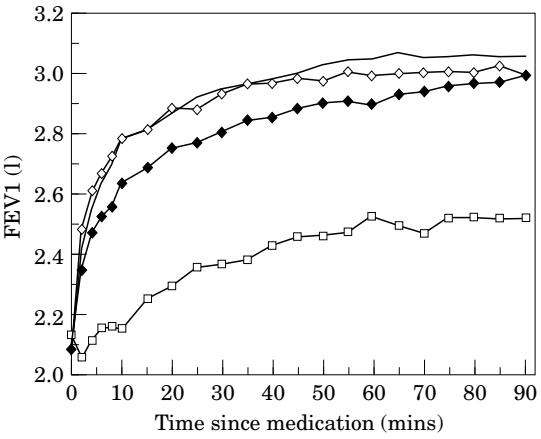

Fig. 1 Geometric mean FEV1 over time on each study medication day. —×—: Formoterol (24 μg); —◇—: salbutamol (400 μg); —◆—: formoterol (12 μg); —□—: placebo.

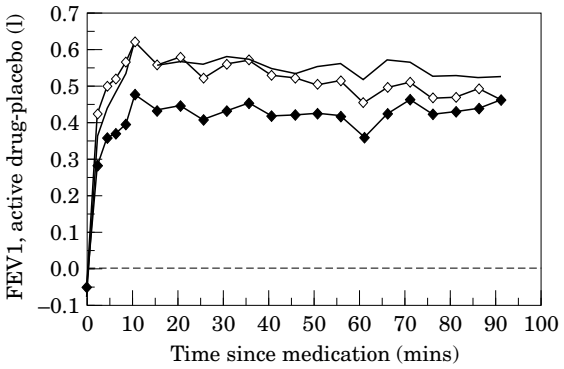

Fig. 2 Differences over time between geometric mean FEV1 after an active medication and that after placebo. —×—: Formoterol (24 μg) − placebo; —◇—: salbutamol (400 μg) − placebo; —◆—: formoterol (12 μg) − placebo.

of mild–moderate severity, mean FEV1 (SD) being 87% (17%) predicted with a range of 60–117%. Most used salbutamol 200 μg from a metered dose inhaler as 'rescue medication' (median cumulative dose, 400 μg daily), and 11 took inhaled corticosteroids regularly (median cumulative dose, 800 μg daily). Two subjects were current smokers, and three were former smokers. Table 1 shows mean baseline FEV1 (pre-methacholine), mean lowest FEV1 achieved (after last dose of methacholine), geometric mean PD20, and the 95% confidence intervals for these values, before each study medication was given. There were no significant differences.

Figure 1 shows mean FEV1 values at each time point after each study medication. All three active medications were superior to placebo throughout, and each produced a clear improvement by the time of the first FEV1 measurement at 2 min.

Figure 2 shows the difference at each time point between the mean FEV1 obtained following an active medication and that following placebo. Marked bronchodilator effects were apparent for all active medications within 2 min, all reaching a peak within 10 min. The further improvements in FEV1 evident thereafter from Figure 1 can be attributed to the decaying bronchoconstrictor effect of methacholine.

Table 2 shows the mean times following each study medication to regain 50% and 80% of the methacholine-induced decrements in FEV1, and the maximum mean FEV1 values attained during the 90 min surveillance period, with 95% confidence intervals. Recoveries of 50% were attained in all but two instances, both following placebo medication; but recoveries of 80% were not achieved by 11 subjects following placebo, by one subject following formoterol 12 μg, and by one subject following formoterol 24 μg. Recovery periods of 95 min were arbitrarily assigned in these circumstances, and so the mean period of recovery by 80% following placebo (and the width of the confidence interval) is likely to be underestimated.

After allowing for differences between the first, second, third, and fourth tests (i.e. an order effect), there were significant differences between the four study medications at both 50% ($F_{3,42}=43.25$, $P<0.001$) and 80% ($F_{3,42}=57.2$, $P<0.001$) recovery points. This was largely explained by the difference between placebo and the mean of the three active medications (50% recovery: $F_{1,42}=170.85$, $P<0.001$; 80% recovery: $F_{1,42}=128.77$, $P<0.001$). There were no significant differences at the 50% recovery point between salbutamol 400 μg and formoterol 24 μg ($F_{1,42}=0.02$, $P=0.9$), nor between formoterol 12 μg and formoterol 24 μg ($F_{1,42}=0.8$, $P=0.4$); and there were similarly no significant differences at the 80% recovery point

Table 2 Mean times in min to regain 50% and 80% of methacholine-induced decrements in FEV1 and mean maximum FEV1 values following study medications (with 95% confidence intervals).

	Placebo	Salbutamol 400 μg	Formoterol 12 μg	Formoterol 24 μg
Mean time to regain:				
50% of decrement	53.1 (46.3–59.9)	6.4 (0–13.2)	10.2 (3.4–17.0)	5.7 (0–12.5)
80% of decrement	83.3 (75.0–91.6)	17.4 (9.1–25.7)	22.1 (13.8–30.4)	18.0 (9.7–26.3)
Maximum mean FEV1 (l)	2.62 (2.52–2.71)	3.10 (3.00–3.20)	3.05 (2.95–3.14)	3.14 (3.04–3.24)

Confidence intervals derived using standard errors of mean from analysis of variance.

between salbutamol 400 μg and formoterol 24 μg ($F_{1,42}=0.01$, $P=0.9$), nor between formoterol 12 μg and formoterol 24 μg ($F_{1,42}=0.5$, $P=0.5$).

Similarly, there were significant differences between the four study medications in maximum FEV1 attained ($F_{3,42}=23.3$, $P<0.001$), and again this was largely explained by the difference between placebo and the mean of the three active medications ($F_{1,42}=68.15$, $P<0.001$). There were no significant differences between salbutamol 400 μg and formoterol 24 μg ($F_{1,42}=0.4$, $P=0.5$), nor between formoterol 12 μg and formoterol 24 μg ($F_{1,42}=0.3$, $P=0.6$). Thus, the three active medications produced significantly more bronchodilation than placebo at all time points, but no significant differences could be detected between them.

Mean time elapsing before the maximum FEV1 was attained did not differ significantly between placebo and the mean of the three active medications, because this (and the maximum FEV1 itself) depended on the prolonged duration of action of methacholine (and on its continuing decay throughout the surveillance period) in addition to the bronchodilator effect of the active medications.

There were no serious adverse effects which could be attributed to any of the study treatments, and all were well tolerated.

DISCUSSION

All three active medications produced a greater degree of bronchodilatation than placebo throughout the 90 min surveillance period following the methacholine test. Thus all three are effective bronchodilators. Furthermore, all three had a similarly rapid onset of action, producing similar and substantial levels of bronchodilation within 2 min of inhalation and peak bronchodilation within 10 min. Although formoterol 12 μg appeared minimally less effective than formoterol 24 μg (or salbutamol 400 μg), the differences in mean FEV1 (100–150 ml) were not found to be statistically significant and are not likely to be of much clinical significance. The effects of formoterol 24 μg and salbutamol 400 μg appeared almost identical over the 90 min surveillance period, and we would agree with other investigators that the respective doses are approximately equipotent.[4–6,9,11]

Our findings consequently confirm that single doses of the active dry powder formulations are effective (and rapidly so) for mild/moderate degrees of bronchoconstriction when delivered via the Aerolizer™ inhaler. These conclusions should not, however, be extrapolated to the regular use of these medications, since differential down-regulation and tachyphylaxis may then exert an influence. Furthermore, the Aerolizer™ inhaler was used in particularly favourable circumstances. The mean FEV1 values following the methacholine tests all exceeded 2 l and so impairment of inspiratory flow is unlikely to have posed an important problem in drug delivery. With greater degrees of bronchoconstriction this may not be so.

It is of some interest that all three active treatments appeared to produce their maximum effects within 10 min. Improvements in FEV1 thereafter were largely attributable to the decaying bronchoconstrictor effect of methacholine. This period of decay was prolonged, and after 90 min the persisting effect of methacholine was considerable. This justifies the routine use of bronchodilator medication following positive tests.

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