Bronchodilating effects of cumulative doses of formoterol from a novel multi-dose inhaler (Airmax®)

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Abstract The bronchodilating properties of formoterol from a novel multi-dose inhaler, Airmax® 6 µg and from a single-dose dry powder inhaler Foradil® Aeroliser® 12 µg were investigated in 31 adult asthmatics with FEV₁ ≥60% predicted and a reversibility ≥12%. Patients received on a single day four doses of formoterol: cumulative dose 6, 12, 24 and 48 µg from Airmax, or 12, 24, 48 and 96 µg from Aeroliser®. The mean FEV₁ (SD) from baseline to 1 h after the final cumulative dose increased by 0.81 l from 2.62 (0.58) to 3.43 l (0.70) with Airmax® and by 0.85 l from 2.65 (0.60) to 3.51 (0.68) with Aeroliser®. All 90% CIs for all four dose comparisons were within the equivalence range ±0.1 l. There was a higher incidence of hypokalaemia and hyperglycaemia at highest doses during treatment with the Aeroliser® than with Airmax®. In conclusion, formoterol delivered from Airmax® provides a dose-dependent bronchodilating effect which is similar to that obtained by Aeroliser® at double the dose.

INTRODUCTION Long-acting β₂-agonists are used in asthma as an adjunct to anti-inflammatory therapy, increasing long-term control of symptoms, reducing frequency of exacerbations and improving quality of life (1–3). Formoterol is a long-acting β₂-agonist with a fast onset of action comparable to that of salbutamol and a duration of action of up to 12 h (4,5). It has been developed for delivery by inhalation, both by pMDI and by dry powder inhaler (DPI). Airmax® is a novel inhaler (Fig. 1) which utilises proprietary technology known as the X-ACT™ system (active-metering, cyclone-separator technology) designed to provide accurate and consistent dosing largely independent of inspiratory flow-rate (6). The inhaler has a dose reservoir containing 60 doses of formoterol at two strengths 6 and 12 µg, is resistant to humidity and is equipped with a dose counter. In vitro gravimetric and multistage liquid impinger assessments with formoterol Airmax® have shown high dose consistency (relative standard deviations between 2.5 and 3.5%), and emitted doses close to European label claim (7). The mean fine particle dose or the respirable dose (<5.8 µm) delivered from Airmax® formoterol 6 µg strength is 2.5 µg (7). This is similar to that from the single-dose inhaler Aeroliser® (i.e. 2.1 µg) at double the dose, i.e. 12 µg per actuation (8). The aim of this study was to assess and compare the bronchodilating effects of formoterol from the multidose inhaler Airmax® with formoterol from the single-dose inhaler Foradil® Aeroliser® at a 1:2 dose ratio.

METHODS

Patients Eligible study participants, selected from the outpatient department of a hospital and from a GP practice in the Netherlands, were adults (aged 18–45 years) with a documented clinical history of asthma of at least 6 months, a FEV₁ of ≥60% of the predicted normal value for age, height and gender (2l) and FEV₁ reversibility of ≥12% after administration of salbutamol (400 µg) from a pMDI via a spacer device (Volumatic®, GlaxoSmithKline). Patients were excluded if they had received oral corticosteroids or any other investigational medication within the previous 3 months, or had received emergency treatment or been hospitalised.
for asthma within this period. On each treatment day, patients were not to have used bronchodilators in the previous 12 h.

**Study design**

The study was conducted according to an open, randomised, two period crossover design in accordance with the Declaration of Helsinki (South Africa, October 1996) and was approved by the local independent ethics committee. Eligible patients, having given written informed consent, were randomised to their first treatment at the first visit, receiving the alternate treatment at the following visit 2–14 days later. Seven to 14 days thereafter, a follow-up visit post-study took place. On each treatment day patients received four cumulative doses of formoterol at the following time points: 0 (baseline), 70, 140 and 210 min. Doses given from the Aeroliser® were 12, 12, 24 and 48 µg, representing cumulative doses of 12, 24, 48 and 96 µg, whilst doses from the Airmax® were half of the above, i.e. 6, 6, 12 and 24 µg representing cumulative doses of 6, 12, 24 and 48 µg. FEV₁ was measured 1 h post each dose and 10 min before first dose and at 15 min post first dose. In order to exclude non-responders on a particular study day, the study visit of patients failing to demonstrate an increase of FEV₁ of ≥12% 15 min after the first dose was deferred for up to 7 days.

**Safety assessments**

Vital signs and a 12-lead electrocardiogram were recorded at each clinic visit, both before and after dosing.

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**Fig. 1.** Diagram of Airmax® with stage 1 (active metering) and stage 2 (cyclone separator).
on the two treatment days. Routine biochemical and haematological parameters were also assessed on each study day. A complete physical examination was carried out at screening and at the post-study visit. Adverse events were reported at each of the post-screening visits.

**Statistical analyses**

The analysis was performed on the per protocol population consisting of all patients who complied with the protocol without any major deviations. Four pairwise comparisons were conducted by analysis of variance (ANOVA), one for each cumulative dose level. The dependent variable was the absolute change (or percentage change) in FEV$_1$ 1 h after each dose, with patient, visit and treatment as fixed factors. Conventional 90% confidence intervals for equivalence were computed around the differences in response at each dose level. Power calculations required a minimum of 27 patients to be included into the analysis in order to achieve a power of 80% to show equivalence on all four dose comparisons assuming a standard deviation of 3% in FEV$_1$.

**RESULTS**

From medical records, 31 patients were invited to participate, all of whom were randomised to treatment, and comprised the safety population. One patient was lost to follow-up after the first treatment day (with Airmax®) and hence the per protocol efficacy population comprised the 30 patients. Patient demographic data and main concomitant asthma medications are shown in Table 1.

The mean FEV$_1$ (SD) from baseline to 1 h after the final cumulative dose increased by 0.81 l from 2.62 (0.58) to 3.43 l (0.70) with Airmax® and by 0.85 l from 2.65 (0.60) to 3.5 l (0.68) with Aeroliser® (Fig. 2). This corresponds to a mean maximum percentage increase of 32.4 and 34.0% after Airmax® and Aeroliser®, respectively. Onset of action was rapid and 15 min after the first dose mean FEV$_1$ had increased by 19.2% with Airmax® 6 μg and by 20.8% with Aeroliser® 12 μg. The 90% CIs for all four dose comparisons were within the equivalence range ±0.1 l and within ±5% (Table 2). Fifteen adverse events (10 mild, five moderate), all considered to be unlikely to relate to study treatment, were reported by 10 patients. Post-dosing serum potassium levels and blood glucose were below normal in five patients and above normal in eight patients, respectively on Airmax®. On Aeroliser® 10 patients had a drop in serum potassium levels and 16 patients had a rise in blood glucose. In only two patients (both on Aeroliser®) the serum potassium levels were below 3.2 mmol/l and considered clinically relevant. There were no clinically relevant changes in blood pressure or heart rate. There were no clinical abnormalities in the ECG except for biphasic T-top due to low potassium in the two patients.

**DISCUSSION**

In this study formoterol delivered by the multi-dose inhaler Airmax® provided a rapid and dose-related bronchodilation in adult asthmatic patients. The results suggest that formoterol given via Airmax® is approximately equipotent to formoterol given via Aeroliser® at double the dose. This is in line with in vitro pharmaceutical data showing a respirable (or fine particle) dose of formoterol approximately twice as high with Airmax® than with Aeroliser®.

The dose–response effect of formoterol on the degree of bronchodilation was sustained and consistent with observations from previous studies (9,10) being comparable between the two devices at all time points. The results were supported by an analysis of percentage changes in FEV$_1$ which showed that when based on per-

**Table 1.** Patient demographics

<table>
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<th>N</th>
<th>All</th>
<th>31</th>
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<tr>
<td>Mean age (±SD) years</td>
<td>30.4 (8.0)</td>
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<td>Range</td>
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<td>Males:females (N)</td>
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<td>Caucasian: Asian (N)</td>
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<td>Mean weight (±SD) kg</td>
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<td>51–105</td>
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<tr>
<td>Range (cm)</td>
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<tr>
<td>Mean height (±SD) cm</td>
<td>173.2 (74)</td>
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percentage changes the difference at each dose level lay entirely within the range [−5%, +5%]. The cumulative dose–response design has been widely employed in the assessment of bronchodilator drugs since its first introduction in 1973 (11). After single doses of a short-acting inhaled β2-agonist a plateau is reached after approximately 30 min (12), in contrast to the effect of cumulative doses in which a continuous increase in elicited effect is seen, even at doses higher than the normal clinical doses (13) an effect which may be related to increased peripheral lung deposition resulting from the bronchodilation produced by the initial dose.

In the present study formoterol 6 μg from Airmax® and 12 μg from Aeroliser® displayed a very similar and rapid onset of action and 15 min post first dose increased FEV₁ by an average of 20%. Other studies (14,15) have observed that whilst peak FEV₁ values were not different between varying doses of formoterol, onset of action is faster and duration of action is longer when comparing 6 μg with 12 and 24 μg. Therefore, in order to confirm the 1:2 dose relation between Airmax® and Aeroliser® further studies comparing duration of action at different doses are still required.

The systemic effects observed with inhaled formoterol were dose-related. There were twice as many patients with hypokalaemia and hyperglycaemia in the Aeroliser® group compared to the Airmax® group after the maximum dose of formoterol was administered. The administration of formoterol at half the dose from Airmax® could therefore offer some safety advantages over Foradil Aeroliser®, but this should be confirmed in long-term studies.

In conclusion, formoterol 6–48 μg delivered from the multi-dose inhaler Airmax® provides a dose-dependent clinically significant bronchodilating effect which is similar to that obtained by the single-dose inhaler Aeroliser® at double the dose.

Acknowledgements

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<table>
<thead>
<tr>
<th>Treatments</th>
<th>Airmax® (μg)</th>
<th>Aeroliser® (μg)</th>
<th>Lower</th>
<th>Difference</th>
<th>Upper</th>
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<tr>
<td>6</td>
<td>12</td>
<td>−0.08 (−3.6%)</td>
<td>−0.02 (−0.6%)</td>
<td>0.05 (2.5%)</td>
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<td>12</td>
<td>24</td>
<td>−0.10 (−4.7%)</td>
<td>−0.04 (−1.6%)</td>
<td>0.03 (1.4%)</td>
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<tr>
<td>24</td>
<td>48</td>
<td>−0.09 (−4.1%)</td>
<td>−0.03 (−1.1%)</td>
<td>0.04 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>96</td>
<td>−0.10 (−4.6%)</td>
<td>−0.04 (−1.6%)</td>
<td>0.03 (1.5%)</td>
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REFERENCES