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Efficacy and tolerability of formoterol in elderly patients with reversible obstructive airways disease

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This study has compared the efficacy and tolerability of formoterol (FORADIL) dry powder and salbutamol in elderly patients with reversible obstructive airways disease (ROAD). A total of 262 elderly outpatients with clinically stable ROAD participated in a multicentre, double-blind, parallel study. Patients were randomized in equal numbers to receive formoterol 12 μg b.i.d. formoterol 24 μg b.i.d. or salbutamol 400 μg q.i.d. for a 3 month period. All study drugs were inhaled through an Aeroliser™ device. Daily morning and evening peak expiratory flow (PEF) values, symptom scores and additional bronchodilator use were recorded by the patients throughout the study. Clinic assessment which included spirometry and PEF measurements was made at 4, 8 and 12 weeks. Morning and evening PEF values were significantly higher with both doses of formoterol compared with salbutamol. This difference was statistically significant both for the overall study period and during the week preceding each of the clinic visits (4, 8 and 12 weeks). There was no significant difference for the two doses of formoterol with respect to PEF values. The FEV_1 and FVC values between the three treatment groups were similar. The daily use of rescue medication was significantly lower for the formoterol 24 μg group compared with the salbutamol group. The percentage of patients rating the therapeutic effect as 'very good' was significantly higher for formoterol: 41% on 12 μg; 34% on 24 μg; 19% on salbutamol. All treatments were well tolerated. This study demonstrates that formoterol 12 μg and 24 μg b.i.d. by dry powder inhalation are equally effective and are both significantly superior to salbutamol 400 μg q.i.d. in the treatment of ROAD in the elderly.

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Introduction

The introduction of long-acting β_2-agonists has been an important development in the treatment of obstructive airway diseases (1). The main advantage over short-acting β_2-agonists is their prolonged duration of action of at least 12 h. Long-acting β_2-agonists can be given twice daily and provide better control of nocturnal and early morning symptoms of asthma. Formoterol is a potent long-acting selective β_2-agonist which is both effective and well tolerated in patients with asthma (2). It produces bronchodilation of rapid onset which lasts for at least 12 h (3–6). Formoterol has been developed for inhalation as an aerosol from a metered-dose inhaler (MDI) and more recently as a dry powder formulation.

Dry powder delivery systems do not require the patient to co-ordinate the actuation of the device with inhalation and so are often found by patients to be easier to use than MDIs (7). The problems of co-ordination and compliance with inhaled therapy may be a particular concern in the elderly. Therefore, in elderly asthmatic patients requiring a long-acting β_2-agonist to control symptoms a twice-daily regime administered by a dry powder delivery system may be particularly appropriate. However, data on the effects of long-acting β_2-agonists in the elderly is relatively limited (8). Specific studies in the elderly are necessary to assess both tolerability, since this may differ from that in younger patients, and efficacy, since the response to β_2-agonists may decline with age (9). Dose ranging studies with formoterol from both an MDI and a dry powder delivery system have demonstrated that 12 μg b.i.d. is the optimal dose in adults and children (4,5,10,11). There is a suggestion in some studies that elderly patients might derive greater benefit from the 24 μg dose. This study, therefore, compares the efficacy, tolerability and patient acceptability of two doses of formoterol dry powder, 12 μg b.i.d. and 24 μg b.i.d., with salbutamol 400 μg q.i.d. over a 3 month period in elderly patients with reversible obstructive airways disease (ROAD).

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Methods

PATIENTS

A total of 262 elderly male and female patients (aged 64–82 years) with ROAD such as asthma or chronic obstructive

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TABLE 1. Summary of patients' characteristics

	Formoterol 12 μg; $n=83$	Formoterol 24 μg; $n=91$	Salbutamol 400 μg; $n=88$
Mean age (years)	71 (64–82)	71 (64–79)	70 (65–80)
Sex			
Male	70%	56%	55%
Female	30%	44%	45%
Smoking			
Smoker	16%	12%	15%
Non-smoker	25%	22%	28%
Ex-smoker	58%	66%	57%
Predicted FEV_1 (l)	2·4 (1·3–3·3)	2·3 (1·2–3·6)	2·3 (1·2–3·6)
Observed FEV_1, pre-β_2-agonist (l)	1·4 (0·4–3·2)	1·3 (0·5–3·1)	1·3 (0·5–3·2)
FEV_1, post-β_2-agonist (l)	1·7 (0·4–3·3)	1·6 (0·6–3·4)	1·6 (0·7–3·3)

Ranges in parentheses.

TABLE 2. Comparison of overall mean PEF values between treatments

	Treatment difference estimate ($l\ min^{-1}$)	95% CI
Morning		
Formoterol 24 μg *vs.* salbutamol	33·6*	21·0–46·2
Formoterol 12 μg *vs.* salbutamol	33·3*	20·3–46·2
Formoterol 24 μg *vs.* formoterol 12 μg	0·3	− 12·6 to 13·2
Evening		
Formoterol 24 μg *vs.* salbutamol	29·7*	18·3–41·1
Formoterol 12 μg *vs.* salbutamol	32·3*	20·5–44·1
Formoterol 24 μg *vs.* formoterol 12 μg	− 2·6	− 14·2 to 9·1

*$P<0·001$.

pulmonary disease (COPD) with a degree of reversible obstruction participated in the study. Patients were recruited from hospital outpatient clinics and from general practice.

Patients had to be clinically stable and had to have been using inhaled short-acting β_2-agonists for at least 1 month prior to the start of the study. At the screening visit the FEV_1 value (forced expiratory volume in 1 s) had to be at least 40% of the predicted normal level. Patients were required to demonstrate either an improvement of at least 15% in FEV_1 15–30 min after inhalation of a β_2-agonist (dose equivalent to 400 μg dry powder or 2·5 mg nebulized salbutamol) or a difference between morning and evening PEF values (peak expiratory flow) of greater than 15% on at least 3 days of a 2 week run-in period prior to randomization. All subjects gave written consent to participation in the study which was approved by the relevant local Ethics Review Boards.

STUDY DESIGN

The study was multicentre, double-blind, comparative and parallel designed. After the screening visit, all oral and inhaled β_2-agonist therapy was discontinued and patients were given salbutamol 400 μg q.i.d. administered by a dry powder device for a 2 week run-in period. Other airway medication remained unchanged. Following the run-in period patients were randomized in equal numbers to receive formoterol 12 μg b.i.d., formoterol 24 μg b.i.d. or salbutamol 400 μg q.i.d. for a 3 month period. Treatments were allocated on the basis of a randomized code and patients were entered sequentially. All medication was administered using a dry powder device (Aeroliser™ Italseber Farmaceutici, Italy). Patients randomized to formoterol took active treatment in the morning and evening. At midday and bedtime a placebo capsule containing lactose with an identical outward appearance was used. Patients randomized to salbutamol took active medication in the morning, at midday, in the evening and at bedtime. Each patient was provided with a salbutamol (200 μg) Ventolin Rotahaler as rescue medication.

Patients recorded the highest of three PEF values before dosing each morning and evening using a Mini-Wright peak flow meter. Daytime and night-time asthma symptoms were recorded on a diary card daily using a four-point scale

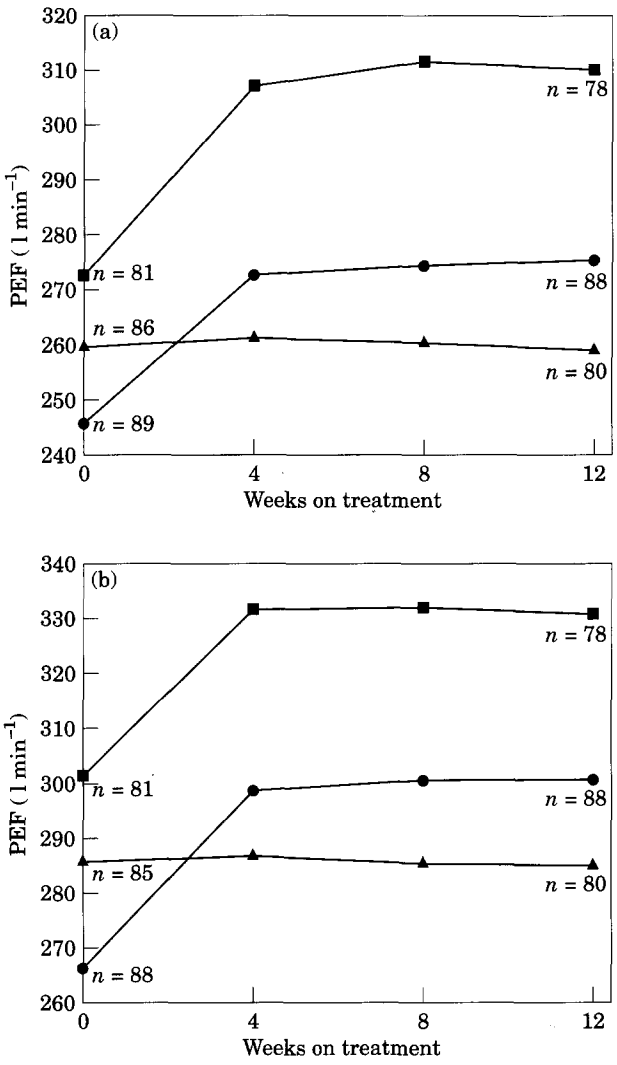

FIG. 1. (a) Morning and (b) evening mean PEF values during the week before each clinic visit in patients receiving formoterol 12 μg (■), formoterol 24 μg (● or salbutamol 400 μg q.d.s (▲).

(from 0, meaning no symptoms, up to 3, for symptoms occurring at rest with no relief afforded by rescue medication). Clinical assessments were made at 4, 8, and 12 weeks of treatment. At these visits FEV_1 and FVC (forced vital capacity) were measured using a dry wedge spirometer (Vitalograph, U.K.). PEF measurements, physical examination, blood tests (haematological and biochemical) has an ECG were also carried out. At the final clinical visit (12 weeks), an overall assessment of therapeutic effect and tolerability was made by the patient and the investigator according to a four-point scale (poor, fair, good, very good).

STATISTICAL METHODS

Treatments were compared independently for morning and evening PEF values, using analysis of covariance (ANCOVA) with baseline PEF value, centre and sex included in the analysis. The patient's mean PEF results for the three treatments taken over the entire double-blind period were compared without carrying forward data for missing days or trimming highest and lowest values. Treatments were also compared with respect to PEF values during the 7 days prior to clinic visits at 4, 8 and 12 weeks. In this case, final observations were carried over for missing data and the trimmed mean was used if data were available for at least 3 days. The patient's mean daily use of rescue medication and asthma scores were analysed using the van Elteren test stratified by centre (12). Logarithmically transformed FEV_1 and FVC values were analysed using ANCOVA. Overall scores for therapeutic effect and tolerability were compared between treatments using logistic regression. Assessment of therapeutic control was analysed using ANCOVA. All statistical tests were two sided and carried out at the 5% significance level.

Results

PATIENTS

A total of 262 patients were randomized. There were no important differences in demographic and baseline data between the three treatment groups (Table 1) including airway medication, concomitant diseases and other medication. Prior to the study 96% of patients were receiving short-acting β_2-agonists and 6% were receiving long-acting β_2-agonist therapy. Of the patients, 88% were receiving inhaled corticosteroids with 11% receiving oral prednisolone. The study was completed by 198 patients (76%). Of the 64 patients who discontinued the study prematurely, 21 were receiving formoterol 12 μg, 16 were receiving formoterol 24 μg and 27 were receiving salbutamol. Only 14 patients in total discontinued treatment prematurely owing to an adverse event (five on formoterol 12 μg, one on formoterol 24 μg and eight on salbutamol). Eight patients discontinued treatment due to an unsatisfactory effect (two on formoterol 12 μg, two on formoterol 24 μg and four on salbutamol). The remaining patients discontinued for non-treatment-related reasons.

PEF

Formoterol 12 μg and 24 μg produced significantly higher morning and evening PEF values during the 3 month study period compared with salbutamol (Table 2). There was no significant difference between the two doses of formoterol with respect to overall morning or evening PEF values. For all time points during the week preceding each clinic visit both doses of formoterol produced significantly higher morning and evening PEF values than salbutamol (Fig. 1 and Table 3). There were no significant differences between formoterol 12 μg and formoterol 24 μg doses.

RESCUE MEDICATION

The mean daily number of additional puffs of rescue medication was significantly lower over the study period for

TABLE 3. Comparison of PEF values between treatments during the week before examination

	Morning		Evening	
	Treatment difference (l min^{-1})	95% CI	Treatment difference (l min^{-1})	95% CI
4 weeks				
F24 *vs.* Sal	30·6*	15·9–45·3	29·0*	14·9–43·1
F12 *vs.* Sal	26·8*	11·7–41·9	26·5*	12·0–41·1
F24 *vs.* F12	3·8	−11·1 to 18·7	2·5	−11·9 to 16·8
8 weeks				
F24 *vs.* Sal	32·1*	16·7–47·5	30·3*	16·4–44·3
F12 *vs.* Sal	38·1*	22·1–54·0	32·2*	17·7–46·8
F24 *vs.* F12	−6	−21·6 to 9·6	−1·9	−16·1 to 12·3
12 weeks				
F24 *vs.* Sal	38·9*	22·7–55·1	30·6*	15·0–46·1
F12 *vs.* Sal	37·7*	20·5–54·1	31·9*	15·8–48·1
F24 *vs.* F12	1·6	−14·8 to 18·1	−1·4	−17·1 to 14·4

*$P<0·001$. F12, formoterol 12 μg; F24, formoterol 24 μg; Sal, salbutamol.

TABLE 4. Mean asthma symptom scores

	Formoterol 12 μg ($n=76$)	Formoterol 24 μg ($n=88$)	Salbutamol 400 μg ($n=83$)
Day time	0·52	0·37	0·49
Night-time	0·26	0·22	0·32
Sleep disturbance	0·27	0·24*	0·33

*$P=0·06$ compared with salbutamol.

the group receiving formoterol 24 μg (0·58 puffs) compared with those receiving salbutamol (0·85 puffs, $P=0·045$). No significant difference was seen between formoterol 12 μg (0·80 puffs) cmpared with salbutamol.

ASTHMA SYMPTOM SCORES

In all three treatment groups there was an improvement in mean daytime and night-time asthma scores and mean sleep disturbance scores (data not shown). Mean values were better in the formoterol 24 μg group (Table 4. However, no differences between the treatments for any of these three variables reached statistical significance.

CLINIC ASSESSMENT OF LUNG FUNCTION

PEF values measured at 4, 8, and 12 week clinic visits showed very similar results to those recorded by the patients at home. Significantly higher PEF values were seen for formoterol 12 μg and formoterol 24 μg compared with salbutamol at all clinic visits ($P<0·05$). There were no significant differences between the two doses of formoterol.

At all clinic visits there were no significant differences between the three treatment groups with respect to FEV_1 or FVC values (data not shown).

PATIENTS' AND INVESTIGATORS OVERALL ASSESSMENT OF EFFICACY

Patients' assessment of therapeutic effect at the end of the study was significantly better for the two formoterol doses compared to salbutamol ($P<0·02$, Table 5). No significant differences between treatments were found for the investigators' assessment of efficacy (data not shown).

TOLERABILITY

All three treatments were well tolerated. Formoterol 12 and 24 μg were both better tolerated than salbutamol with respect to the number of patients experiencing drug-related adverse events and events leading to discontinuation of therapy. Fourteen patients (17%) taking formoterol 12 μg, 20 patients (22%) taking formoterol 24 μg and 23 patients (26%) taking salbutamol experienced drug-related adverse events. of these, one patient taking formoterol 12 μg and

TABLE 5. Patient assessment of overall therapeutic effect

	Formoterol 12 μg (n=76)	Formoterol 24 μg (n=88)	Salbutamol 400 μg (n=83)
Very good	31 (41%)	30 (34%)	16 (19%)
Good	22 (29%)	40 (45%)	39 (47%)
Fair	19 (25%)	16 (18%)	18 (22%)
Poor	4 (5%)	2 (2%)	10 (12%)

Significant difference between treatments: formoterol 24 μg *vs* salbutamol, P=0·002; formoterol 12 μg *vs* salbutamol, P=0·017.

one patient taking salbutamol experienced events classified as serious (chest pain and syncope with supraventricular tachycardia, respectively). Only 14 patients in total discontinued prematurely owing to adverse events. Five patients discontinued treatment in the formoterol 12 μg group owing to individual cases of depression, malaise, arthralgia, bronchitis and asthma. One patient discontinued in the formoterol 24 μg group because of headache. Eight patients discontinued in the salbutamol group [headache, chest pain, asthma (three), chest infection, tremor, syncope]. No clinically significant findings were seen over the study period with respect to vital signs, laboratory values or ECG recordings. Patients' and investigators' overall assessment of tolerability at the final visit showed no significant differences between the three treatments but 'very good' ratings were more often recorded for formoterol 12 μg (41%) and formoterol 24 μg (34%) than for salbutamol (19%).

Discussion

This study has demonstrated in a group of elderly patients with ROAD that the long-acting β_2-agonist formoterol when administered by a dry powder inhalation was more effective than inhaled salbutamol in improving PEF values. The results confirm in an elderly population previously reported findings in younger adult asthmatic patients that formoterol 12 μg and 24 μg b.i.d. are significantly more effective than regular inhaled salbutamol (13,14). The study demonstrates that the optimal dose for the elderly is the same as for adults (12 μg b.i.d.) as there is no significant additional benefit in terms of efficacy for the higher dose, 24 μ,g b.i.d. This does not provide support for the suggestion that responsiveness to inhaled β_2-agonists declines with age (9), which would warrant the use of higher doses.

This is the first study that has examined the safety and tolerability of formoterol dry powder inhalation in an elderly population with ROAD. The results show that formoterol 12 μg and 24 μg inhaled twice daily from the Aeroliser® is a well-tolerated bronchodilator in the elderly. Fewer patients taking formoterol 12 μg experienced drug-related adverse reactions compared with formoterol 24 μg, suggesting that this dose may be better tolerated overall. The use of long-acting β_2-agonists by dry powder inhalation may be particularly appropriate in elderly patients because of the twice-daily regimen and the ease of use of a breath-actuated inhaler. However, data on the use of these drugs in the elderly remain limited.

Regular treatment with long-acting β_2-agonists has been reported to cause a reduction in bronchodilator β_2-agonist responses (15–18) and a decrease in the degree of protection against exercise (19) and methacholine-induced bronchoconstriction (15). Our protocol was not designed to investigate the effects of chronic dosing with formoterol on acute bronchodilator and bronchoprotective responses. The improvement in PEF values produced by formoterol, however, was maintained throughout the 12 weeks of the study.

In conclusion this study shows that the optimal dose of formoterol in the elderly is the same as for other adults. It demonstrates that formoterol given by dry powder inhalation is superior in terms of both efficacy and tolerability to salbutamol in the treatment of elderly patients with ROAD.

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