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Formoterol Monotherapy Compared with Combined Ipratropium Bromide plus Fenoterol in the Treatment of Chronic Obstructive Pulmonary Disease

Martin Konermann,[1] *Rainer Suchantke,*[1] *Jürgen Mogck,*[1] *Jens Brauburger,*[2] *Matthias Bräutigam*[2] and *the Study Group*[*]

1 Department of Internal Medicine, Marienkrankenhaus Kassel, Kassel, Germany
2 Novartis Pharma GmbH Nürnberg, Germany

* For a list of participants, see page 241.

Abstract

Objectives: To compare the efficacy and tolerability of formoterol (12 or 24μg twice daily) alone with combined ipratropium bromide and fenoterol in the treatment of chronic obstructive pulmonary disease (COPD).

Design and Setting: Randomised, parallel-group, open-label study in 10 German centres.

Patients: 101 patients with COPD.

Interventions: The patients were randomised to receive either formoterol 12μg twice daily or a combination of ipratropium bromide 20μg plus fenoterol 50μg three times daily for 4 weeks. Dosages could be doubled if required.

Results: Morning pre-dose airway resistance (R_{eff}) decreased significantly from 0.87 to 0.66 kPa•L^{-1}•s with formoterol and from 0.81 to 0.66 kPa•L^{-1}•s with combined ipratropium bromide and fenoterol (p = ns). The treatment groups were similar with respect to other lung function parameters, daily clinical symptom scores and salbutamol rescue medication. Adverse events occurred in 7/52 (13.5%) of the formoterol and 11/49 (22.4%) of the combination therapy group, and were the reason for study discontinuation in one (1.9%) versus seven (14.3%) patients. The overall discontinuation rate was 5.8% (3/52) with formoterol and 20.4% (10/49) with ipratropium bromide/fenoterol (p = 0.038).

Conclusions: The efficacy of formoterol monotherapy was comparable with that of combined ipratropium bromide and fenoterol in the treatment of COPD. Formoterol had a better adverse event profile and a lower rate of discontinuations resulting from adverse events.

Chronic obstructive pulmonary disease (COPD) is a major illness that has a prevalence of 4 to 6% in the adult male population in the United States. In 1991, COPD was the fourth most common cause of death with a mortality rate of 18.6 per 100 000 of the population.[1,2] COPD is also one of the most frequent causes of worker disability and early retirement arising from ill health.[3] The primary aetiology of COPD is cigarette smoking,[4] but exposure to inhaled toxic substances or homozygosity for α_1 antitrypsin deficiency are also rare causes.[5]

The primary symptom of COPD is dyspnoea, a result of permanent airway obstruction. This initially occurs on exertion, but later occurs at rest as the disease progresses.[6] It differs from bronchial asthma in which airway obstruction is reversible and symptom-free periods also occur.[1,6] A proportion of asthmatics over the age of 40 years develop COPD.[7]

The goals of therapy are symptom control, maintenance of the best possible lung function and avoidance of exacerbations. The basis of this is the removal of aetiological factors, particularly smoke inhalation.[8] Medical therapy is based primarily on systemic or inhaled bronchodilators, of which various combinations of inhaled β-sympathomimetics and anticholinergics have been shown to be effective.[9-13] A disadvantage of these fixed combinations is the short half-life of inhaled anticholinergics, which realistically can only be combined with similarly short-acting β-sympathomimetics.[14] This necessitates three- to four-times-daily drug administration. The long-acting inhaled β_2-adrenoceptor agonists, which have been proved to be effective in asthma, require a less frequent drug administration regimen and provide better compliance and symptom control.[15]

In two large international studies, the long-acting β-adrenoceptor agonist formoterol has been shown to be superior to placebo, theophylline and ipratroprium bromide.[16-18] A comparison with the commonly used fixed combination of an inhaled anticholinergic and a short-acting β-adrenoceptor agonist has not been performed to date.

The aim of the present study was to examine the efficacy and tolerability of the inhaled selective long-acting β_2-adrenoceptor agonist, formoterol, in patients with COPD, compared with the fixed combination of inhaled ipratroprium bromide and fenoterol.

Materials and Methods

Study Design

This was a prospective, open-label, multicentre, randomised, parallel-group comparison of formoterol monotherapy with a fixed combination of ipratroprium bromide and fenoterol. Patients were assessed during a screening visit, at which time demographic and tolerability parameters were recorded. The study duration was 4 weeks in total, and patients returned to the study centre for assessment of lung function and tolerability at 1-week intervals.

The study was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent for participation in the study, which was approved by the local ethics committees.

Patients

Patients aged ≥40 years with COPD with an airway resistance (R_{eff}) >0.5 kPa•L^{-1}•s were eligible for the study. The following exclusion criteria were applied: current or previous diagnosis of asthma, COPD exacerbation within 1 month of screening, extended domiciliary oxygen requirement, significant concomitant diseases or abnormal baseline laboratory values, corrected QT-interval (QT_c) >0.46s, intolerance of β_2-adrenoceptor agonists or inhaled medications, treatment with study medication within the last month, and vaccination against pneumococcal and/or influenza infection within 1 month of screening. Pregnant or breast-feeding women were excluded, and all female participants had to use an acceptable method of contraception for the duration of the trial. Use of COPD medications necessitated a sufficient washout: systemic corticosteroids (1 month), theophylline (72 hours),

anticholinergics (48 hours), oral or inhaled long-acting β_2-adrenoceptor agonists (48 hours), inhaled short-acting β_2-adrenoceptor agonists (6 hours), β-blockers (1 month), and drugs influencing myocardial conduction (1 month).

Study Medication

Patients who were on a stable dose of inhaled corticosteroids could continue this treatment throughout the study. At the baseline visit eligible patients were randomised to receive either formoterol 12μg twice daily in a dry powder inhaler (Foradil®, Novartis, Basel, Switzerland) or a combination of ipratroprium bromide 20μg and fenoterol 50μg three times daily in a metered-dose inhaler (Berodual® MDI, Boehringer Ingelheim, Germany). For symptomatic relief during the trial, patients were permitted to take inhaled salbutamol via a metered-dose inhaler as rescue medication.

If a patient's airway resistance had not fallen by less than 0.3 $kPa \cdot L^{-1} \cdot s$ after the first week of treatment, the dosage of study medication was doubled. Furthermore, if more than 800μg of rescue salbutamol was required on 6 consecutive days, the study medication dose was also doubled. If the rescue medication requirement was not decreased by this dose escalation, the patient was withdrawn from the trial.

Measurements

Lung Function Data

At each visit (approximately 8am) lung function was measured by body plethysmography before and 15 minutes after the first daily dose of study medication. The following parameters were measured: airway resistance (R_{eff}), specific airway resistance (SR_{eff}), intrathoracic gas volume (ITGV), residual volume (RV), total lung capacity (TLC), vital capacity (VC), forced vital capacity (FVC), inspiratory vital capacity (IVC), peak expiratory flow rate (PEFR), forced expiratory volume in 1 second (FEV_1), maximum expiratory flow (MEF 25, MEF 50, MEF 75), inspiratory capacity (IC) and expiratory residual volume (ERV).

Diary Cards

Patients measured morning and evening PEFR daily and recorded the results on a diary card. The use of rescue medication and symptoms of COPD were also self-assessed and recorded daily. The following COPD symptoms were scored from 0 to 3, in ascending order of severity: ability to perform daily activities, breathlessness, night-time awakening, cough, amount of sputum, breathlessness when getting up, increased sweating.

Tolerability

Patients were questioned about adverse reactions to medication at all study visits. At baseline, week 1 and at the final visit a 12-lead ECG was recorded for at least 10 seconds and blood samples were drawn for biochemical and haematological laboratory tests.

Sample Size Calculation

Forty-two patients per group were required to detect a difference in airway resistance of 0.1 $kPa \cdot L^{-1} \cdot s$, with a standard deviation of 0.16 $kPa \cdot L^{-1} \cdot s$, accepting an α-error of 5% and a β-error of 20%. To compensate for dropouts, 50 patients per group were recruited. The primary efficacy criterion was airway resistance at the end of the study before inhalation of the last dose of study medication. Group comparisons were performed by means of a nonparametric analysis of co-variance (ANCOVA) including the study site as a stratification factor and baseline airway resistance as a co-variant. The other lung function parameters and clinical symptoms were analysed by ANCOVA with baseline as co-variant. The number of days during which rescue salbutamol was required was compared with the van Elteren test. A two-sided p-value of <0.05 using tests of significance was considered significant.

Treatment Assignment

Treatments were assigned according to a predetermined computer-generated randomisation list in a ratio of 1:1. Thus, study treatments were randomly allotted to sequential patient numbers in

balanced blocks of four by centre and investigators then allocated patient numbers sequentially at baseline.

Results

Demographics

A total of 101 patients were enrolled at 10 study centres between May 1999 and March 2000. The baseline characteristics of the two groups were broadly similar, although the formoterol group contained more females and patients had slightly higher COPD severity than the combination group (table I). 5.8% (3/52) of patients randomised to formoterol and 20.4% (10/49) of those randomised to combination treatment were withdrawn from the study ($p = 0.038$). The reasons for withdrawal were adverse events (in one patient on formoterol and in seven patients on the combination), unsatisfactory therapeutic effect (in one patient on formoterol and in two patients on the combination), protocol violation (in one formoterol-treated patient) and administrative problems (in one patient on combined treatment).

Concomitant medication use was similar in both groups. The most frequently used drugs were budesonide and fluticasone, which were taken by 13 and six patients, respectively, in the formoterol group and by 10 and 11 patients, respectively, in the combination group. The mean treatment duration was 27.9 days with formoterol and 26.8 days with combination therapy. Dose escalation was performed in 76.9% (40/52) of the formoterol group compared with 77.6% (38/49) of those receiving ipratroprium bromide/fenoterol.

Efficacy

Lung Function Tests

In both treatment groups there was a significant improvement in airway resistance during the study. R_{eff} decreased from 0.87 to 0.66 kPa•L^{-1}•s (–24%) with formoterol and from 0.81 to 0.66 kPa•L^{-1}•s (–18.5%) with ipratroprium bromide/ fenoterol. Both groups experienced consistent improvements in FEV_1 and PEFR, two important parameters of airway obstruction. No statistically significant differences were noted between the groups on the basis of lung function parameters (table II).

Clinical Symptoms

Patients in both groups had clinical symptoms of COPD on most days of the study. Only 10% of the formoterol group and 6% of the combination therapy group were completely free of clinical symptoms throughout the trial. The accumulated total symptom score during the study was slightly lower in the formoterol group (table III). This was mainly due to less severe shortness of breath during the daytime and when getting up. These intergroup differences in symptoms were not statistically significant.

The mean duration during which rescue salbutamol was required (expressed as a percentage of total treatment time) was 35.5% in the formoterol group and 33.0% in the combination group ($p = ns$).

Table I. Baseline characteristics of the two groups

	Formoterol (n = 52)	Ipratropium bromide + fenoterol (n = 49)
Gender (M/F)	28/24	31/18
%	54/46	63/37
Age (y)	61 (37-83)	61 (41-76)
Weight (kg) ± SD	83 ± 19	83 ± 17
Airway resistance (kPa•L^{-1}•s) ± SD	0.86 ± 0.44	0.80 ± 0.46
Peak flow (%) ± SD[a]	53.8 ± 20.4	53.8 ± 19.8
FEV_1 (%) ± SD[a]	58.7 ± 23.8	52.9 ± 20.1

a Percentage of predicted value.

FEV_1 = forced expiratory volume in 1 second.

Table II. Baseline values and changes in R_{eff}, FEV_1 and PEF from baseline to the measurement before the last morning dose of formoterol or ipratropium bromide + fenoterol at the end of the study (EOS)[a]

	Formoterol (n = 50)	Ipratropium bromide + fenoterol (n = 47)
R_{eff} (kPa•L^{-1}•s)		
Baseline	0.87 ± 0.44	0.81 ± 0.47
EOS	0.66 ± 0.49	0.66 ± 0.41
Change from baseline	-0.21 ± 0.39	-0.15 ± 0.46
FEV_1 (L)		
Baseline	1.55 ± 0.58	1.51 ± 0.58
EOS	1.68 ± 0.61	1.63 ± 0.66
Change from baseline	0.13 ± 0.40	0.12 ± 0.42
PEF (L/s)		
Baseline	3.82 ± 1.52	3.98 ± 1.59
EOS	4.42 ± 1.91	4.68 ± 1.86
Change from baseline	0.60 ± 1.30	0.70 ± 1.48

a Two patients from each group were excluded from the intent-to-treat analysis because they had no value for R_{eff} after the first intake of study medication.

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; **R_{eff}** = airway resistance.

Table III. Cumulated symptom score from patient diaries during study treatment. Values are given as means ± SD

Symptom	Formoterol (n = 50)	Ipratropium bromide + fenoterol (n= 46)
Total score	285 ± 174	301 ± 145
Days with symptoms (%)	89.9 ± 22.5	94.0 ±18.2
Affecting daily life score	50.1 ± 42.2	48.1 ± 34.3
Days with this symptom (%)	66.7 ± 39.2	76.0 ± 35.6
Shortness of breath score	50.6 ±36.7	59.8 ± 29.7
Days with this symptom (%)	72.4 ±37.2	87.8 ± 23.2
Nocturnal awakening score	27.3 ± 26.3	29.9 ± 36.5
Days with this symptom (%)	54.6 ± 40.7	53.3 ± 41.2
Coughing score	60.3 ± 40.3	57.8 ± 39.5
Days with this symptom (%)	73.8 ± 36.9	76.8 ± 35.4
Sputum quantity (ml/day)	45.8 ± 38.9	42.8 ± 31.4
Days with this symptom (%)	64.1 ± 41.1	67.7 ± 39.9
Shortness of breath when getting up	23.1 ± 27.1	34.7 ± 31.5
Days with this symptom (%)	46.0 ± 43.2	65.1 ± 41.3
Increased sweating score	27.9 ± 37.5	26.5 ± 31.2
Days with this symptom (%)	39.2 ± 40.8	42.7 ± 42.0

Tolerability

Adverse events were reported in 13.5% (7/52) of those treated with formoterol and in 22.4% (11/49) of the patients taking combination therapy. One patient in the formoterol group and seven patients (14.3%) in the combination therapy group withdrew from the study because of adverse events ($p < 0.01$).

The adverse events that led to study withdrawal were infections in three patients including the formoterol-treated patient, respiratory tract-related events in three patients, and events related to the gastrointestinal system, central and peripheral nervous system and myocardium, respectively. No significant effects on ECG parameters, vital signs or laboratory blood tests were seen in either group during the trial.

Discussion

This study demonstrates equivalent efficacy of the long-acting β_2-adrenoceptor agonist formoterol and the combination of the anticholinergic drug ipratroprium bromide and the short-acting β_2-adrenoceptor agonist fenoterol in COPD. In terms of tolerability, more adverse events were reported on combination therapy, leading to significantly more withdrawals.

Patients in this study had continuous symptoms of COPD and were clearly in need of long-term therapy. At present, standard treatment for these patients is a combination of an anticholinergic and a β_2-adrenoceptor agonist, such as used in this study.[19] Combining the β_2-adrenoceptor agonist and ipratroprium bromide in a metered-dose inhaler helps to simplify therapy and aid compliance. However, this form of combination therapy needs to be administered at least three times daily. Reduction of the administration frequency to twice daily may aid compliance, particularly in everyday outpatient management.[20]

The long-acting β_2-adrenoceptor agonist formoterol combines a rapid onset of action with a long-lasting bronchodilatory effect, and needs to be taken only twice daily.[21] For this reason formoterol was considered as an attractive alternative for the treatment of patients with COPD. In another study formoterol proved to be more effective than ipratroprium bromide monotherapy.[17] We did not show superiority of formoterol over the combination of ipratroprium bromide and a short-acting β_2-adrenoceptor agonist. However, it is noteworthy that there was a clear difference in favour of formoterol regarding the number of adverse events and the incidence of premature treatment withdrawals.

Although there was only a small difference in the clinical symptom score between the treatment groups, it is interesting that the patients in the formoterol group had 15 to 20% fewer days with symptoms related to breathlessness than the patients with combination therapy. There is evidence that the beneficial effects of β_2-adrenoceptor agonists on the symptoms of COPD are not always correlated with a similar improvement in measured lung function.[22]

This is one of the few multicentre studies using airway resistance as the main efficacy parameter for the assessment of the efficacy of β_2-adrenoceptor agonists in COPD. In most studies FEV_1 or PEF was chosen as the main lung function parameter for feasibility reasons, as body plethysmography is not widely available. However, forced expiratory manoeuvres are required for FEV_1 and PEF assessment, which can lead to early airway collapse and decreased airflow. This may underestimate bronchodilatory effects occurring more peripherally in the respiratory tract, which is the major site of airway resistance in COPD.[23] As a result of reduced expiratory transpulmonary pressures occurring during body plethysmography, dynamic airway compression is smaller and airflow can be measured more accurately.[24] In our study R_{eff} had high sensitivity for the detection of treatment effects (particularly for formoterol), whereas PEF had intermediate sensitivity and FEV_1 had low sensitivity. Numerically, the improvement in R_{eff} with formoterol was 24%, while PEF and FEV_1 increased by only 15.7% and 8.4%, respectively.

A shortcoming of this study was that it was not double blind, because of technical problems in producing a placebo to match the ipratropium bromide/fenoterol combination for a double-dummy design. However, airway resistance is a rather objective parameter and randomisation did not result in significant imbalances between the treatment groups.

Because of the small sample sizes, the numerical equivalence of the two treatments in terms of efficacy could not be substantiated by statistical equivalence testing. Further studies on larger numbers of patients and using additional methods like the distance-walking test and blood gases are needed to finally determine the place of formoterol in COPD treatment recommendations relative to combination therapy with anticholinergics and β_2-adrenoceptor agonists.

Conclusions

In conclusion, this study confirms the importance of formoterol monotherapy in the treatment of COPD and supports the use of airway resistance as a more sensitive lung function parameter than FEV_1 for the assessment of β_2-adrenoceptor agonist effects in COPD.

Study Participants

R. Balzer (Gummersbach), *F.-J. Berger* (Düren), *W. Feu*βner (Kassel), *A. Iwantscheff* (Frankfurt/M), *C. Kellner* (Hagen), *J. Martinez* (Köln), *N. Peslis* (Eschwege), *H. Samiri* (Frankfurt/M), *K.-H. Schuster* (Schweinfurt).

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Correspondence and offprints: Pd Dr *Martin Konermann*, Marienkrankenhaus, Marburger Strasse 85, 34127 Kassel, Germany.
E-mail: MKH-Kassel.Konermann@t-online.de