A dose-response study with formoterol Turbuhaler® as maintenance therapy in asthmatic patients

A.J.M. Schreurs*, H.E.J. Sinninghe Damsté**, C.S. de Graaff+, A.P.M. Greefhorst++

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ABSTRACT: The aim of this randomized, double-blind, parallel group study was to determine the lowest effective dose of 6, 12 and 24 μg formoterol fumarate dihydrate Turbuhaler _b.i.d._ compared with placebo.

The 4 week treatment was preceded by a 1 week run-in period. Morning peak expiratory flow (PEF) before intake of the study drug was the primary variable. Patients recorded PEF, prior to and 15 min after intake of the study drug (immediate response), asthma symptoms, and use of rescue medication morning and evening. Of 221 patients (71 females and 150 males), 194 were included in the efficacy per protocol (PP) analysis; mean age 47 yrs, mean forced expiratory volume in one second (FEV_1) 2.01 L (58% of predicted), mean FEV_1 reversibility 27% at entry. Ninety percent used inhaled steroids.

Compared with placebo, 6 μg formoterol _b.i.d._ was found to be the lowest effective dose in the morning (p=0.008) and evening (p=0.0041) PEF. The mean increases in PEF were 22 and 23 L·min^{-1} respectively, compared with placebo. After 6 μg formoterol, the mean immediate increase in morning PEF was 42 L·min^{-1} compared to an increase of only 9 L·min^{-1} after placebo (p<0.0001). All doses produced a statistically significant decrease in asthma symptoms, day and night, and the need for rescue medication at night. All doses were well-tolerated.

In conclusion, the lowest effective dose in this study was formoterol Turbuhaler 6 μg _b.i.d._
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*Dept of Pulmonology, Onze Lieve Vrouwe Gasthuis, Amsterdam, NL. **Dept of Pulmonology, Twenteborg Ziekenhuis, Almelo, NL. +Dept of Pulmonology, Medisch Centrum Alkmaar, Alkmaar, NL. ++Dept of Pulmonology, Streekziekenhuis Midden Twente, Hengelo, NL.

Correspondence: A.J.M. Schreurs, Onze Lieve Vrouwe Gasthuis, P.O. Box 95500, 1090 HM Amsterdam, The Netherlands

Current practice recommends the use of inhaled β$_2$-adrenoceptor agonists in the management of acute and chronic asthma [1]. However, the bronchodilating effect of most β$_2$-agonists is short, therefore necessitating frequent inhalations up to four times daily to maintain adequate efficacy. This is especially a problem at night, when the duration of action is not sufficiently long to prevent nocturnal bronchoconstriction and early morning dyspnoea [2]. Patients are also liable to have an inferior sleep quality, with much time spent awake or in light sleep stages [3].

The prospects of improvements in maintenance therapy of these and other patients are enhanced with the introduction of longer-acting β$_2$-agonists [4]. Formoterol represents a new class of β$_2$-agonists. It is highly β$_2$-adreno-receptor selective, with a rapid onset comparable to that of terbutaline and salbutamol but with a longer duration of action. It provides good efficacy with _b.i.d._ dosing [5–10], and may, therefore, also have the possibility to improve compliance.

The literature available on the use of inhaled formoterol refers to chlorofluorocarbon (CFC) propellant-driven pressurized metered-dose inhalers (pMDIs). The recommended doses of formoterol pMDI are 12 or 24 μg _b.i.d._ [6–9]. Recent advances in drug delivery systems have led to the introduction of dry powder, inspiratory flow driven inhalation devices, such as Turbuhaler®. Turbuhaler has proved to be capable of delivering a higher proportion of drug particles to the lung than pMDIs, thus inducing an increased effect of budesonide, terbutaline and salbutamol [11–15]. Formoterol Turbuhaler has been investigated after single dose administrations of 6, 12 and 24 μg to asthmatics [16]. The findings confirmed the immediate onset and prolonged duration of action, indicating the feasibility of _b.i.d._ dosing. The bronchodilating effect and onset of action of formoterol by dry powder inhalation in maintenance therapy are under investigation. This randomized, placebo-controlled study was designed to identify the lowest effective dose of 6, 12 and 24 μg formoterol fumarate Turbuhaler (hereafter called "formoterol") that, when given _b.i.d._ for 4 weeks, significantly differs from placebo in its bronchodilating effect 12 h after administration.

Material and methods

Study subjects

Out-patients suffering from moderate asthma defined according to the American Thoracic Society (ATS) [17] were entered into the study. Patients were of both sexes, aged 18 yrs or older. Patients were required to have had

diagnosed asthma for 6 months or more, and a basal forced expiratory volume during one second (FEV_1) of 1 L or more and between 40–80% of predicted values [18]. A reversibility of FEV_1, of at least 15% after 0.5 mg terbutaline sulphate *via* Turbuhaler was required once during the month before entering the study. Patients were excluded from participation if they had: pronounced seasonal allergy; upper or lower respiratory tract infection within 1 or 4 weeks, respectively of the start of the study; evidence of clinically relevant diseases; or uncontrolled hyperthyroidism. Pregnant or lactating women were excluded. Patients on β-blocker therapy (including eyedrops) or with hypersensitivity to $β_2$-agonists were excluded, as were patients who were considered unable to comply with the study protocol. Inhaled glucocorticosteroids and disodium cromoglycate were allowed at a constant dose 4 weeks prior to and during the study.

Study design

The trial was a randomized, double-blind, placebo-controlled study in parallel groups receiving 4 weeks of treatment. Fifteen clinics, all in The Netherlands, participated. Following a 1 week run-in period, when patients recorded baseline symptoms and peak expiratory flow (PEF) measurements, patients were allocated to 4 weeks of treatment with 6, 12 or 24 μg formoterol or placebo administered every 12 h. Inhalation was performed by dry powder delivery (Turbuhaler; Astra Draco AB, Lund, Sweden). Prior to inclusion, patients discontinued their ordinary asthma medication at agreed times. During the study, the following drugs were not allowed: oral $β_2$-agonists, oral steroids, xanthines, antihistamines, anticholinergics and inhaled $β_2$-agonists except for inhaled terbutaline (Bricanyl® Turbuhaler® 0.25 mg·dose⁻¹) to be used when needed.

Methods

At home, using a mini-Wright peak flow meter (linear scale), patients measured morning and evening PEF before and 15 min after taking the study medication (immediate response) and entered the values (best of three attempts) in diary cards. Patients were requested not to take any rescue medication 6 h prior to a PEF reading. If medication was used, this was noted on the diary card. In addition, asthma symptoms, use of rescue medication and adverse events were recorded on diary cards. Asthma symptoms defined as breathlessness, chest tightness, wheeziness or cough with or without sputum were scored on a scale of 0 to 3, where: 0 was no symptoms; 1 was mild, easily tolerated symptoms; 2 was moderate and discomforting symptoms enough to cause interference with usual, daily activity; and 3 was severe and incapacitating symptoms with inability to perform usual daily activity.

Patients visited the clinic before and after the run-in period and every second week of the treatment period. They were telephoned or a personal contact was made 2 weeks after treatment ended to inquire about adverse events. At each clinic visit, before 9.30 a.m., spirometry tests were performed prior to intake of study medication and at least 6 h after last use of rescue medication. The highest values of three measurements of FEV_1 and forced vital capacity (FVC) were recorded. In addition medications were reviewed, diary cards were collected, and sitting blood pressure and pulse were measured at each visit. At the first and final visits, electrocardiograms and blood samples for routine biochemistry were also taken. In some patients (n=16), additional serum potassium determinations were made before and 2 h after study drug intake at baseline, and after 2 and 4 weeks of treatment.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the Ethics Committees of all participating centres. Signed informed consent was obtained from all patients before enrolment.

Analysis

The primary variable was the change in morning PEF from the run-in period to the treatment period. At 80% power, 50 patients per group (200 in total) were required to detect a true mean difference in change in morning PEF of about 28 L·min⁻¹ in a pairwise comparison using a two-tailed t-test at 5% significance level, given a standard deviation in morning PEF change of about 50 L·min⁻¹.

In addition to morning and evening PEF, the immediate response to the study drug, defined as the change from before to 15 min after the study drug intake was measured. The change in PEF from before to 15 min after study drug intake, *i.e.* immediate response, was calculated for each patient in the treatment period. For all these variables, mean values (adjusted for centre and treatment-by-centre interaction effects) over the periods were calculated for each patient, using data from Day 4 and onwards to allow for patients to reach steady-state. For FVC and FEV_1, measured at the clinic, changes from run-in to treatment (the mean of the two visits) were used as variables in the analysis. Comparisons between treatments were based on an analysis of variance (ANOVA) model with the factors: treatment, centre, and treatment-by-centre interaction. The lowest significant dose was identified by comparing formoterol from the highest to lowest dose with placebo until a nonsignificant result was obtained. If a low dose differed significantly from placebo, the additional effect of the 24 μg dose given *b.i.d.* was examined, by comparing 24 μg to each other dose from the lowest to the highest until the first nonsignificant result was obtained. The diurnal variation in PEF before inhalation of study medication during the treatment period was defined as $100 \times$ (evening PEF-morning PEF)/evening PEF.

Results

This multicentre study involved 15 sites and enrolled 236 patients. Fourteen patients were never randomized; eight patients failed to meet the inclusion criteria, three were noncompliant with study procedures, and three deteriorated in their asthma during the run-in period. Thus, 222 patients were included and randomized.

The efficacy data were analysed according to the per protocol (PP) approach. Twenty eight patients were considered not evaluable for this analysis for the following

Table 1. – Patient disposition and baseline characteristics in the 3 dose groups and placebo group

| | | Formoterol *b.i.d.* | | |
	Placebo	6 µg	12 µg	24 µg
Patients n	51	47	47	49
Age yrs	50 (16)	45 (14)	48 (16)	46 (16)
Body weight kg	75 (13)	75 (10)	76 (15)	76 (12)
Sex M/F	40/11	30/17	31/16	33/16
Smoking history past or current/never	25/26	27/20	30/17	25/24
Pulmonary function				
FEV1 preterbutaline L	2.00 (0.66)	2.01 (0.56)	1.99 (0.66)	2.07 (0.79)
FEV1 post-terbutaline L	2.53 (0.78)	2.52 (0.67)	2.51 (0.91)	2.71 (0.93)
FEV1 reversibility % above initial	27 (9)	27 (11)	26 (17)	32 (18)
FEV1 preterbutaline % pred	58 (13)	58 (12)	58 (13)	57 (13)
Run-in diary data				
Morning PEF L·min⁻¹	362 (106)	355 (90)	355 (101)	380 (111)
Evening PEF L·min⁻¹	380 (106)	376 (91)	376 (105)	412 (117)
Daytime symptoms score	0.71 (0.58)	0.81 (0.71)	0.85 (0.63)	0.78 (0.60)
Night-time symptoms score	0.60 (0.52)	0.72 (0.70)	0.58 (0.57)	0.72 (0.59)
Daytime terbutaline doses n	1.5 (1.2)	1.5 (1.4)	2.2 (2.1)	2.0 (1.6)
Night-time terbutaline doses n	1.1 (0.9)	1.1 (1.1)	1.4 (1.3)	1.5 (1.3)

Values are presented as mean, and SD in parenthesis. M: male; F: female; FEV1: forced expiratory volume in one second; %

reasons: reversibility <15% (n=5); FEV1 outside predicted ranges (n=8); no valid data during run-in period (n=7); prohibited medication taken prior to the reversibility test (n=3); use of steroids not according to protocol (n=3); poor compliance (n=1); and failure to take any study medication after randomization (n=1). Thus, 194 patients were included in the efficacy PP analysis, but all 221 patients who used the study medication were included in the safety analysis.

Patient disposition and baseline characteristics

The disposition and baseline characteristics of patients per dose group and placebo group are described in table 1. Mean age of the patients was 47 yrs. FEV1, at entry was 2.01 L (58% of predicted). The mean reversibility was 27%. Inhaled steroids were used by 90% of patients. There was no imbalance between the groups concerning demography, medical history, FEV1 and FVC. The group of patients treated with formoterol 24 µg *b.i.d.* had a greater basal morning and evening PEF compared to the other groups, however, this was not tested for significance.

Daily PEF measurements

The mean changes from the run-in period to the treatment period in morning and evening PEF 12 h after the dose are presented in table 2, whilst the daily means over the run-in and treatment periods are shown in figures 1 and 2. Formoterol 6 µg *b.i.d.* was found to be the lowest effective dose in morning PEF *vs* placebo (p=0.008), and the mean treatment difference between placebo and formoterol 6 µg was 22 L·min⁻¹. The mean additional effect of increasing the dose from 6 µg to 24 µg was 15 L·min⁻¹ which, however, was found to be nonsignificant (p=0.067). For evening PEF, formoterol 6 µg *b.i.d.* was also found to be the lowest effective dose *versus* placebo and the mean treatment difference was 23 L·min⁻¹ (p=0.004). Increasing the dose from 6 to 24 µg *b.i.d.* gave an additional effect of 18 L·min⁻¹ (p=0.035). There was no statistically significant difference between the 6 and 12 µg *b.i.d.* doses. For all treatment groups including placebo, the diurnal variation in PEF was very low and varied between 3.4 to 5.5%.

During the treatment period, the immediate bronchodilating response of formoterol and placebo was also

Table 2. – Change in lung function, asthma symptom score and use of rescue medication in the 4 groups from run-in to treatment period

| | | Formoterol *b.i.d.* | | |
	Placebo	6 µg	12 µg	24 µg
Morning PEF L·min⁻¹	-3 (30)	18 (39)	17 (42)	33 (41)
Evening PEF L·min⁻¹	-7 (27)	14 (40)	20 (35)	32 (36)
FEV1 L	0.01 (0.26)	0.13 (0.32)	0.20 (0.35)	0.16 (0.33)
FVC L	0.08 (0.36)	0.14 (0.38)	0.19 (0.42)	0.08 (0.41)
Asthma symptom score				
Daytime	0.15 (0.51)	-0.21 (0.55)	-0.41 (0.50)	-0.34 (0.52)
Night-time	0.12 (0.47)	-0.24 (0.55)	-0.24 (0.43)	-0.33 (0.45)
Rescue inhalations n				
Daytime	-0.64 (1.08)	-0.77 (1.42)	-1.30 (1.45)	-1.42 (1.52)
Night-time	-0.32 (0.79)	-0.72 (0.98)	-0.80 (1.00)	-0.94 (1.14)

Values are presented as mean, and SD in parenthesis. PEF: peak expiratory flow; FVC: forced vital capacity; FEV1: forced expiratory volume in one second.
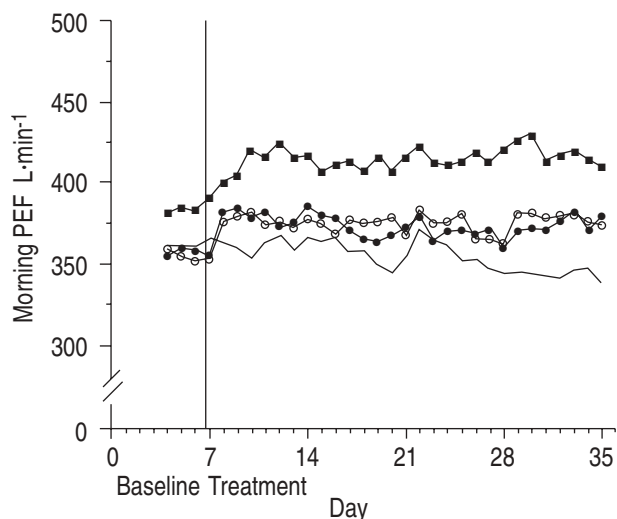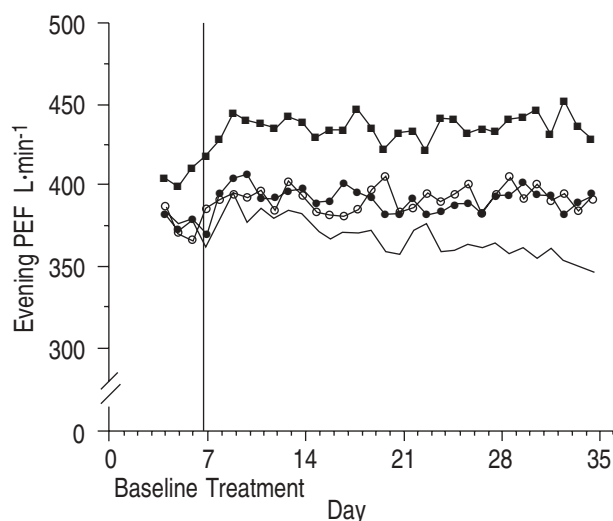
Fig. 1. – Daily means of predose (≈12 h after previous dose intake) morning peak expiratory flow (PEF) over the run-in and treatment periods. ——— : placebo; —●—: formoterol Turbuhaler® 6 µg; —○— : formoterol Turbuhaler® 12 µg; —■—: formoterol Turbuhaler® 24 µg.

Fig. 2. – Daily means of predose (≈12 h after previous dose intake) evening peak expiratory flow (PEF) over the run-in and treatment periods. ——— : placebo; —●—: formoterol Turbuhaler® 6 µg; —○—: formoterol Turbuhaler® 12 µg; —■—: formoterol Turbuhaler® 24 µg.

measured. The mean immediate response to the drug in the morning and evening was on average 9 and 3 L·min⁻¹, respectively, for placebo, compared with >40 and >35 L·min⁻¹ respectively, for all doses of formoterol (fig. 3). In the comparisons of immediate responses to drug in morning and evening PEF, formoterol 6 µg was found to be the lowest effective dose (p<0.0001). Increasing the dose did not increase the magnitude of response. Neither the immediate effect nor the predose PEF values changed during the 4 weeks of treatment.

FEV1, and FVC

Basal FEV1, and FVC values were similar for all groups prior to treatment. For FEV1, the mean changes from run-in to treatment were numerically consistently higher for all formoterol doses compared with placebo and were of the same magnitude. The treatment difference between
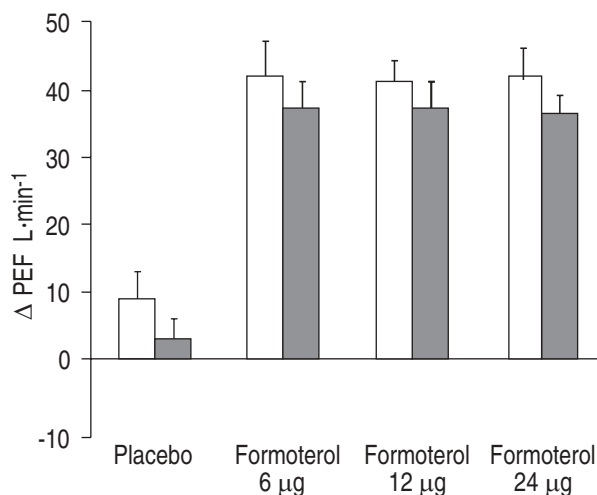

Fig. 3. – Mean change (SEM) of immediate response in morning peak expiratory flow (PEF) (▢) and evening PEF (▨) 15 min after placebo, 6, 12 or 24 µg formoterol Turbuhaler® *b.i.d.*

the highest dose and placebo (0.15 L) did not reach statistical significance (p=0.056) (table 2 and fig. 4). In the corresponding analyses of FVC, no effect of formoterol was found, *i.e.* the difference between placebo and formoterol 24 µg *b.i.d.* was not statistically significant (table 2).

Daily asthma symptom scores

Compared with placebo, all formoterol doses gave consistent improvements from the run-in period both in daytime and night-time asthma symptoms (table 2). Formoterol 6 µg *b.i.d.* was found to be the lowest effective dose (daytime: p=0.001; night-time: p<0.001). No additional improvement was shown by increasing the dose from 6 to 24 µg

Use of rescue medication

Patients were instructed to use 0.25 mg terbutaline by inhalation when needed during run-in and treatment. A
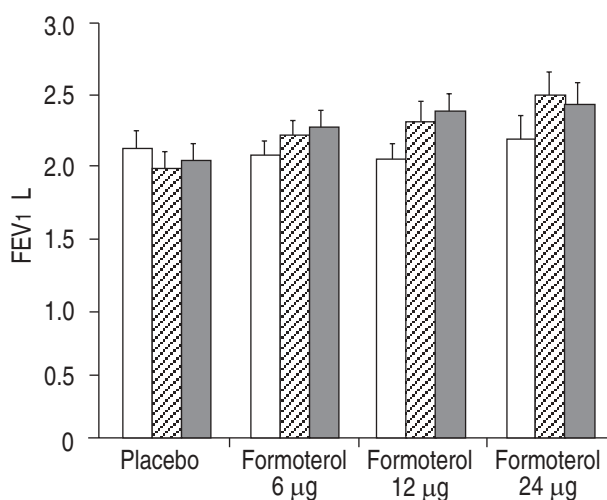

Fig. 4. – Mean predose (≈12 h after previous dose intake) FEV1 (SEM) in the morning prior to (▢) and after 2 weeks (▨) and 4 weeks (▨) of treatment with placebo, 6, 12 or 24 µg formoterol *b.i.d.* FEV1: forced expiratory volume in one second.

decrease in the need for this rescue medication was observed in all treatment groups (table 2). Compared with placebo, formoterol 12 µg *b.i.d.* was the lowest dose that statistically significantly reduced daytime rescue medication (p=0.019), while 6 µg *b.i.d.* was the lowest dose for night-time rescue use (p=0.034). The number of patients (%) without need for rescue medication during the nights increased from run-in to the last week of the treatment period from 16 to 30%, 19 to 77%, 20 to 66% and 9 to 61% of the patients treated with placebo, 6, 12 and 24 µg formoterol *b.i.d.*, respectively.

Safety

The incidence of adverse events was in general low and of a kind known to occur during treatment with β-agonists. Headache and tremor were the most commonly occurring adverse events and their incidence was dose-related. There were no differences, however, between the lowest dose and placebo. Formoterol had no clinically adverse effect on blood pressure or pulse. There were three "serious adverse events": one patient (6 µg *b.i.d.*) was hospitalized with pneumonia but recovered completely; one patient (12 µg *b.i.d.*) was hospitalized because of asthma deterioration but recovered and was discharged after 6 h; and one patient (6 µg *b.i.d.*) developed a pleomorphic adenoma in the parotid gland 2 months after the end of treatment and was later treated for cancer. These events were not considered to be related to drug therapy. Routine electrocardiogram readings and biochemistry measurements revealed no differences between placebo and formoterol. Additional serum potassium levels were measured before and 2 h after drug intake in a small number of patients (n=16), and showed no clinically relevant changes.

Discussion

The present placebo-controlled study was performed to evaluate the bronchodilatory effect during steady-state conditions of three dose levels of formoterol in patients with mild-to-moderate asthma. In this patient population, approximately 90% of patients used inhaled steroids. Their use of rescue medication during the run-in period was relatively low and the asthma symptoms were scored as mild. FEV_1 was on average 58% of predicted. These patients were, however, candidates for additional β$_2$-agonist therapy, since they responded to the inhalation of a β$_2$-agonist; FEV_1 increased on average by 27% from baseline 15 min after administration of terbutaline.

This study showed that formoterol Turbuhaler in the tested doses was highly efficacious. Peak expiratory flow, measured approximately 12 h after dosing, was significantly improved. Nocturnal and diurnal asthma symptoms were decreased, as was the need for rescue medication. The improved lung function, in combination with less asthma symptoms and need of rescue medication, due to longer duration has previously been demonstrated in a study of formoterol [7], where 24 µg was given *via* pMDI *b.i.d.*. In our study, formoterol 6 µg *b.i.d. via* Turbuhaler was found to be the lowest effective dose for most variables.

Formoterol induced both immediate and prolonged bronchodilatory effects. The increase in PEF 15 min after inhalation of all doses was more than 40 L·min^{-1} in the morning and 35 L·min^{-1} in the evening. The corresponding figures for placebo were 9 and 3 L·min^{-1}, respectively. PEF measurements performed in the morning prior to the next dose of study medication showed on average -3, 18, 17 and 33 L·min^{-1} increase for placebo, 6, 12 and 24 µg, respectively, *versus* the run-in period. These data confirm similar immediate effect and somewhat dose-dependent longer effect of formoterol demonstrated in earlier studies in conventional pMDIs [7, 19–22]. In our study, administration by dry powder inhalation shows 6 µg *b.i.d.* to be the lowest effective dose. This dose is lower than those used in previous dose-effect studies using pMDI devices. Typically 12 and 24 µg doses have been used both in short-term and long-term comparative studies in adults and children [23, 24]. However, two studies indicated that 12 µg doses *via* pMDI may be suboptimal [22, 25]. Turbuhaler administration has been shown to increase the deposition of inhaled drugs in the lungs [11, 13–15]. Thus, there is a prospect of achieving the desired therapeutic effect of formoterol with a lower dose *via* Turbuhaler (however, this has yet to be confirmed) compared with the conventional metered-dose aerosol. In view of the current debate on the role of β-agonist therapy and suggestions that potential adverse effects of short-acting β-agonists are dose-related, it is important to identify the lowest effective dose [26, 27]. In these patients treated with β$_2$-agonists before study start, the effect of formoterol was preserved at the same level during the whole study. Formoterol was well-tolerated by the patients. The incidence of adverse effects was generally low and of a kind known to occur during β$_2$-agonist treatment.

We conclude that *b.i.d.* administration of 6 µg formoterol fumarate Turbuhaler was the lowest significantly effective dose in controlling mild-to-moderate asthma in this study. Although higher doses induced greater effect in absolute numbers, 6 µg increased morning peak expiratory flow up to 12 h after dosing. Six micrograms was also the lowest dose that significantly reduced both the night-time and daytime asthma symptoms, as well as the need for rescue medication during the night.

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