

Short communication

Formoterol inhaled as dry powder or via pressurized metered-dose inhaler in a cumulative dose-response study

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Formoterol administered by a dry-powder (DP) capsule inhaler was compared with a pressurized metered-dose inhaler (pMDI) with regard to bronchodilating and systemic effects. The study used a double-blind, crossover, double-dummy technique. Twelve patients with moderate reversible asthma in a stable phase were examined on two separate study days, and the inhalers were given in randomized order. After baseline measurements, increasing doses of formoterol were given at intervals of 75 min. FEV₁ and heart rate and tremor measurements were repeated after each dose, and the doses were 12 + 12 + 24 + 48 µg, giving a total dose of 96 µg. The peak expiratory flow rate (PEFR) was recorded in the morning before the first dose, after the last dose, and then repeatedly at home until 19 h after the last dose. There was an equal increase in ventilatory capacity at each dose level, independent of inhaler device. Repeated PEFR measurements after the last dose did not reveal any differences in duration of effect. There was a slight but statistically significant increase in heart rate and tremor after the highest doses of the DP formulation compared to the pMDI. These systemic effects can probably be explained by the reduced oral deposition of the aerosol caused by using a spacer. This study indicates that the DP and pMDI formulations of formoterol are equipotent in bronchodilation.

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Formoterol administered via a pressurized metered-dose inhaler (pMDI) is a new β_2 -agonist which has been tested in more than 100 clinical trials including more than 3000 asthmatic patients in Europe, Canada, and the USA. Formoterol has proved to be an effective bronchodilator in patients with reversible obstructive respiratory disease after single doses of 12 or 24 µg (1–4). Formoterol pMDI also has rapid onset of action with a duration of effect of at least 12 h (2, 5). In long-term studies, formoterol has been shown to be effective in a b.i.d. regimen (4, 6–9).

A dry-powder (DP) formulation has been developed to minimize patient coordination difficulties. DP inhalers are also more friendly to the environ-

ment, as Freons are not used. An ISF inhaler (AerolizerTM) has been developed and is now used in clinical practice.

The present study aimed to establish equipotent bronchodilating doses of the DP formulation administered by Aerolizer and by pMDI when inhaled in cumulative doses by patients with moderately severe asthma.

Material and methods

Twelve patients (seven men) aged 21–69 years with moderately severe bronchial asthma in a stable phase were included in the trial. The patients'

asthma had to be reversible by at least 15% after 0.2 mg or 20% (maximum 50%) after 0.5 mg salbutamol (mean 28%, range 15–28) and have a baseline FEV₁ of more than 30% of predicted (mean 71%, range 41–99). If the baseline FEV₁ variability was greater than 15%, the last experiment day had to be repeated later. Methylxanthines, oral sustained release β_2 -agonists, and short-acting inhaled β_2 -agonists were stopped at least 36, 24, and 12 h before the start of the study, respectively. No patients were on long-acting β_2 -agonists. Inhaled corticosteroids were used in all patients but were kept at a stable dosage during the trial period.

Design

The study was of a double-blind, crossover design using a double-dummy technique to keep the treatment blind. The treatments, formoterol DP and formoterol solution aerosol (pMDI) were given in a randomized order. Each patient received four increasing doses of each formulation at 75-min intervals (12 + 12 + 24 + 48 μ g) on two nonconsecutive study days with 3–8 days between. The total dose was 96 μ g. The time interval between the doses was chosen to achieve the near-maximum effect of each dose.

Inhalation device and technique

The doses from the pMDI were inhaled through a large-volume spacer (Volumatic[®]) to optimize the deposition into the airways and to minimize the risk of inhalation faults. Two actuations were given into the spacer, followed by the patients breathing in deeply and slowly and holding their breath for at least 10 s. The doses from the DP formulation were inhaled as capsules from an ISF inhalation device (Aerolizer[®]). After expiration, a deep and fast inhalation was required. Patients were asked to hold their breath for at least 10 s. Placebo was used as the double-dummy for both formulations to ensure blindness.

Procedure

The assessments were made by the same physician at the same time of the day, usually starting at 8 a.m. The patients were studied in the laboratory for 5 h, commencing after the first test dose. Spirometry (FEV₁), heart rate, and tremor were assessed before and 30 and 60 min after each dose. Tremor was recorded by a finger accelerometer method described earlier (10, 11).

Laboratory data were recorded before the first test dose and 60 min after the last dose on each test day. PEF_R was also recorded before the first dose

and 1, 3, 7, 10, or 19 h after the last dose. The PEF_R recordings after 3, 7, 10, and 19 h were performed by the patients at home and recorded in a diary. The last recording was performed early the following morning.

All patients gave their written informed consent to the trial, and the study was approved by the Ethics Committee in Göteborg and the National Board of Health and Welfare (Sweden).

Statistics

The 95% confidence interval (T distribution) for the mean differences between the two treatments at each dose level and time point was calculated. The FEV₁ was expressed as percentage of the highest value obtained on any of the two study days for each subject and calculated at baseline and 60 min after each dose. For the systemic effect variables heart rate and tremor, the values 60 min after dose administration were used. These values tended to be more pronounced than the 30-min values. Mean values ($\pm$ SEM) are presented.

Results

Spirometry

The dose-response curves for FEV₁ after the two formulations were superimposed, and the maximum FEV₁ response was achieved after the highest dose; for DP, 98.3% ($\pm$ 0.5%), and for pMDI, 96.7% ($\pm$ 1%). The effect on FEV₁ was not statistically significantly different between the two formulations at any dose level for the two formulations (Fig. 1).

Systemic effects

At the lower doses (12 and 24 μ g), there were no statistically significant differences between the two formulations in heart rate. However, there was an increasing effect with increasing doses, and with the 48- and 96- μ g doses, heart rate was statistically significantly higher after the DP formulation. The mean difference at the highest dose level (96 μ g) was five beats/min. Tremor expressed as a ratio compared with baseline increased with increasing doses and was statistically significantly higher after the highest dose of DP compared to the pMDI (Fig. 2). However, none of the patients reported subjective palpitations or tremor.

Peak expiratory flow

Only at 10 h after the last dose could a small but statistically significant difference in PEF_R be seen

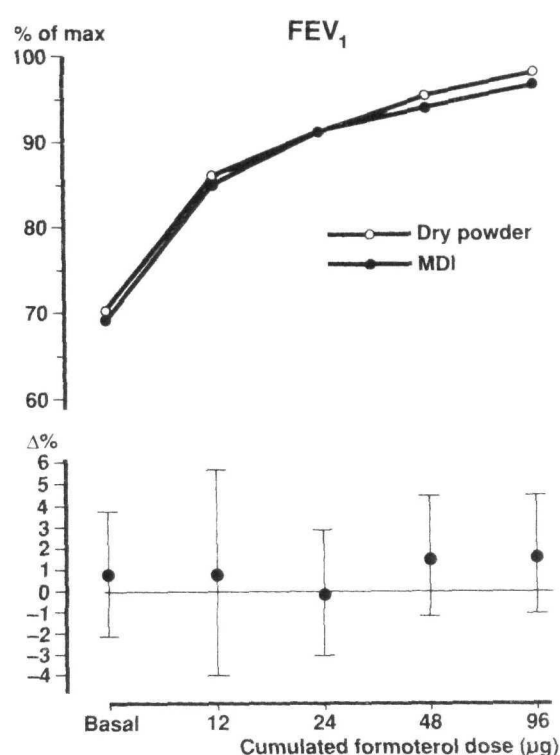


Fig. 1. FEV₁ (percentage of maximum individual value) obtained after inhalation of increasing doses of formoterol pMDI ● and DP ○. Lower panel shows mean difference with 95% confidence interval for difference.

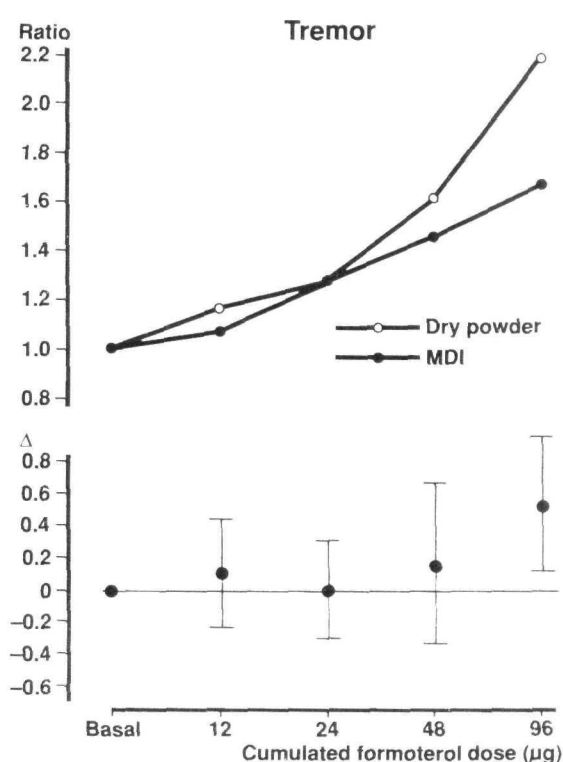


Fig. 2. PEFR (l/min) after inhalation of increasing doses of formoterol. Lower panel shows mean difference with 95% confidence interval for difference.

between the two formulations. As regards the other time points, there were no statistically significant differences between the two formulations, neither at peak effect nor after 19 h of recording.

This study was not designed to evaluate the duration of bronchodilation. However, the PEFR was still statistically significantly higher than baseline ($P < 0.05$) for both treatments at 19 h after the last dose (8–10%). This indicates a duration of

efficacy of more than 12 h after a high dose of formoterol.

Laboratory

Blood samples taken before and after the last dose revealed a slight increase in glucose ($P < 0.05$), which was judged to be of no clinical relevance, and a decrease in P-potassium and B-eosinophils ($P < 0.05$) for both formulations. No other relevant changes were found in any of the laboratory values analyzed. There were no statistically significant differences between the two formulations.

Discussion

This study indicates that the two formoterol formulations used, i.e., DP given through an ISF device and an aerosol given by a pMDI are equipotent in bronchodilating effect. Systemic effects, such as effects on heart rate and tremor, were significantly more pronounced for the DP at the highest dose levels. As the pMDI formoterol was administered via a large-volume spacer in which some of the active substance was deposited, the systemic effects were smaller than when the drug was administered through the DP inhaler in which more drug is deposited in the oropharynx and subsequently swallowed. Thus, the drug was absorbed either from the oropharyngeal mucosa or from the gastrointestinal tract. This is one possible explanation of the increased systemic effects obtained with the DP formulation.

Cumulative dose-response studies have some drawbacks, as the different doses which are tested are not randomized and the effect of one dose may affect the results of the next dose. In our laboratory, as well as in many others, several studies of this design have been performed over the years to test equipotency, and the results have usually been in very good agreement with results from noncumulative dose-finding studies (3, 12). A prerequisite is that the near-maximum effect be achieved within the time interval chosen. We find this design useful for early studies, at least when studying different formulations of a drug or drugs with the same time-effect profile.

To summarize, formoterol given as DP is equipotent µg for µg (1 : 1) to formoterol given as a pMDI through a spacer with regard to bronchodilation but produces somewhat greater systemic effects when given in doses higher than usual (48 and 96 µg).

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