Studies on the bronchodilator, tremorogenic, cardiovascular and hypokalaemic effects of fenoterol dry powder in asthma

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- 1 The airway and tremor response and cardiovascular and hypokalaemic effects of single and cumulative doses of fenoterol given by dry powder capsules (DPC) and by metered dose inhaler (MDI) were studied in asthmatics in two randomized, crossover trials.
- 2 Single doses of fenoterol DPC and MDI (0.2 mg, 0.4 mg), investigated in 24 subjects, produced similar, dose-dependent increases in FEV₁. Fenoterol DPC caused less tremor response and less hypokalaemic effects than fenoterol MDI.
- 3 Cumulative doses of fenoterol DPC and MDI (0.2, 0.6, 1.4, 3.0, 6.2 mg), investigated in 12 subjects, produced a comparable bronchodilatation (mean maximum increase in FEV₁ was $0.53 \pm 0.06/0.52 \pm 0.08$ l for DPC/MDI) and a similar, dose-dependent rise in heart rate ($35 \pm 3.81/41 \pm 2.25$ beats min⁻¹). The rise in tremor and the fall in plasma potassium were smaller after DPC than after MDI. The mean maximum changes were $51.58 \pm 6.41/95.83 \pm 6.75$ cm s⁻² for tremor and $-0.68 \pm 0.09/-0.96 \pm 0.10$ mmol l⁻¹ for potassium.
- 4 Our findings may result from a difference in the pharmacokinetics of the dry powder and the aerosol formulation, particularly differences in distribution and absorption.
- 5 In conclusion, fenoterol DPC used in low therapeutic doses (0.2, 0.4 mg), is preferable to the MDI. Fenoterol DPC used as rescue medication in high cumulative doses, do not suggest a greater safety margin than the MDI and the same restrictions should be considered for the fenoterol dry powder formulation as suggested for the MDI.

Keywords fenoterol dry powder asthma lung function finger tremor plasma potassium

Introduction

Inhaled β_2 -adrenoceptor agonists are the most effective and most widely used bronchodilators for the treatment of asthma. The goal for bronchodilator therapy should be to produce optimal airway response with minimal systemic adverse effects [1].

Fenoterol is a derivative of metaproterenol with relatively selective β_2 -sympathomimetic activity [2]. Recently a possible relationship between the risk for fatal asthma and the use of inhaled β_2 -adrenoceptor agonists, especially fenoterol, given by metered dose inhaler (MDI) has been published [3–7]. Fenoterol MDI may have more hypokalaemic and adverse cardiovascular

effects than related compounds [8–11]. No relevant data have been published previously, however, on the effects of the dry powder formulation of fenoterol on cardiac and metabolic function as well as on skeletal muscle tremor.

Therefore we investigated the acute bronchodilatation, tremor response, cardiovascular, and hypokalaemic effects of single doses (study 1) and cumulative doses (study 2) of inhaled fenoterol given by dry powder capsule (DPC) and by MDI to compare the wanted and unwanted effects of these different formulations in asthmatics.

Methods

Subjects

Twenty-seven patients with a documented history of asthma but no other important disorders were recruited. Twenty-four patients completed study 1 and 12 patients completed study 2 (Table 1). Each subject had a normal electrocardiogram (ECG; 12-lead) and a Holter ECG monitoring Lown Grade 0-I, a forced expiratory volume in 1 s (FEV_1) $\leq$ 60% of the predicted value; a rise in FEV_1 of at least 15% and in tremor amplitude of at least 35% after inhalation of 0.4 mg fenoterol applied by MDI. On each test day FEV_1 had to be within 85% to 115% of the previous evaluation. Regular medication consisted of inhaled treatment only, including a β_2 -adrenoceptor agonist (600–1200 μ g salbutamol daily) and regular inhaled corticosteroids (1000–2000 μ g beclomethasone dipropionate daily). All subjects were experienced in the use of the equipment and in the inhalation technique. All subjects gave informed written consent and the study was approved by the local hospital ethics committee.

Techniques

FEV_1 (best of 3 measurements) and specific airway conductance (sGaw) were measured by a constant volume body plethysmograph (Bodyscreen II, Jaeger, Wuerzburg, Germany). sGaw is the reciprocal of airway resistance corrected for thoracic gas volume and the mean of 5 reproducible traces was used for analysis [12]. All values were corrected to BTPS. Finger tremor was measured by a previously validated method using a piezoelectric accelerometer (Tremometer, Zak, Simbach/Inn, Germany) taped to the terminal phalanx of the right middle finger with the forearm supported and the hand outstretched [13]. Tremor amplitude was assessed as the sum of the integrated signals over a period of 10 s, a mean value was calculated from 4 consecutive measurements. Heart rate was assessed by Holter ECG monitoring (Hewlett Packard, McMinnville, Oregon, USA). Continuous ambulatory recordings of the ECG were made over each observation period. In study 2, an additional rhythm strip recorded on standard leads

I to III of an ECG at 50 mm s⁻¹ (Cardiopan CR-300, Philips, Eindhoven, Netherlands) was performed. Blood pressure was measured with a standard mercury-sphygmomanometer taking the first and the fifth Korotkoff sounds as the systolic and diastolic values, respectively. Plasma potassium concentration was measured by flame photometry with a normal reference range of 3.5–5.0 mmol l⁻¹.

Protocol design

Study 1 (single doses) Twenty-four subjects were studied at the same time of day on 4 nonconsecutive days on which they were given single doses of fenoterol-DPC (0.2 and 0.4 mg) or fenoterol-MDI (0.2 and 0.4 mg) according to a randomized, 4-period, crossover, double-dummy design (Table 1). Patients were asked to stop inhaled β_2 -adrenoceptor agonists 12 h prior to the start of each study day whereas the normal use of inhaled steroids was continued throughout. When the subject arrived an ambulatory ECG monitor was attached and an indwelling cannula was inserted into a forearm vein for blood sampling, the subjects then rested for 30 min. Baseline measurements of all parameters were made and the patients then inhaled the respective study medication. sGaw was registered 1, 3, 5, 7.5, 10, 20, 30, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 h after drug administration. Finger tremor, heart rate and blood pressure were evaluated at the same intervals from 10 min onwards, measurements of FEV_1 were done from 30 min onwards. Blood was taken for measurement of plasma potassium concentration at baseline and after 15 and 30 min, 2 and 12 h.

Study 2 (cumulative doses) Twelve subjects were studied on two occasions on which they were given cumulative doses of fenoterol-DPC or fenoterol-MDI according to a randomized, two-period, crossover design with a washout period of 7 days between treatments. After the same baseline procedure as in study 1, the subjects received 1, 2, 4, 8, and 16 capsules of fenoterol or the respective puffs of fenoterol by MDI with intervals of 60 min to give cumulative doses of 0.2, 0.6, 1.4, 3.0, 6.2 mg. sGaw and FEV_1 were measured 30 and 60 min after each dose; plasma potassium was

Table 1 Demographic data and bronchial reversibility test of the asthmatics who completed study 1 and study 2, respectively

	Study 1 (single dose)	Study 2 (cumulative doses)
Number of patients (women/men)	24 (12/12)	12 (7/5)
Smoking habits (N/E/S)	8/13/3	5/6/1
Age (years)	47.54 $\pm$ 2.40 (21–66)	46.00 $\pm$ 3.85 (21–65)
Duration of asthma (years)	8.29 $\pm$ 1.17 (1–25)	9.75 $\pm$ 2.12 (1–25)
<i>Baseline values</i>		
FEV_1 (l)	1.55 $\pm$ 0.11 (0.80–2.80)	1.57 $\pm$ 0.17 (0.90–2.80)
FEV_1 (% predicted)	48.45 $\pm$ 1.59 (33–60)	50.33 $\pm$ 2.11 (39–60)
sGaw (s ⁻¹ kPa ⁻¹)	0.28 $\pm$ 0.01 (0.18–0.43)	0.30 $\pm$ 0.02 (0.21–0.43)
<i>Post-fenoterol*</i>		
FEV_1 (% change)	32.12 $\pm$ 1.90 (21–51)	30.83 $\pm$ 2.11 (22–43)
sGaw (% change)	176.83 $\pm$ 11.29 (71–275)	166.66 $\pm$ 15.65 (71–244)

Data are mean $\pm$ s.e. mean (range). N: never smoker, E: ex-smoker (> 5 years), S: current smoker.

*0.4 mg applied by metered dose inhaler.

measured 15, 30, 45, and 60 min after each dose; heart rate, rhythm strip, blood pressure and tremor every 10 min after each dose. The maximum changes after each dose were used for calculations. The study was stopped if the heart rate rose above 130 beats min^{-1} .

Subjective effects (tremor, restlessness, palpitations, tussive irritation, cough, dry throat, headache, nausea) were documented after each cumulative dose as either spontaneously reported or reported after direct questioning and these were graded as mild, moderate or severe in nature.

Study drugs Only commercially available preparations of fenoterol were used. The MDI expels 0.2 mg fenoterol per puff, the DPC contains 0.2 mg fenoterol. The DPC was given by the original device (inhalator Ingelheim®, Ingelheim/Rhein, Germany).

Statistical analysis Data are presented as arithmetic mean $\pm$ s.e. mean. The area under the curve was determined using the log trapezoidal rule. The data were analyzed with an analysis of variance model (ANOVA) for a four-period (study 1) and a two-period (study 2) crossover design and statistical differences among the groups were established using the post hoc Neumann-Keuls test. The normality and homogeneity of variance assumptions of the analysis of variance model were tested with the Kolmogorov-Smirnov and the Cochran test. Holter ECG recordings were analyzed for heart rate, ventricular ectopic beats and supraventricular premature beats. Results were assessed by the SPSS programs (SPSS Inc., Chicago, Ill.). Values were considered to be significantly different with P values less than 0.05.

Results

There was no significant change in any of the parameters between the study days of baseline assessment (Tables 2, 3).

Study 1 (single doses)

Three subjects discontinued due to different reasons not related to study medication. Subjects 7 and 13 were excluded because of the development of an upper respiratory tract infection and subject 5 discontinued for personal reasons. The data of 24 patients could be subjected to analysis (Table 1). None of these patients inhaled an additional dose of fenoterol as rescue medication within the 12 h observation period.

sGaw increased in a dose-dependent manner with both formulations from the first minute onwards ($P < 0.05$) (Figure 1). The mean $\pm$ s.e. maximum increases in sGaw were $90 \pm 9.89\%$ for MDI 0.2 mg and $170 \pm 13.12\%$ for MDI 0.4 mg compared with $115 \pm 20.19\%$ for DPC 0.2 mg and $172 \pm 10.32\%$ for DPC 0.4 mg. The significant rise in sGaw lasted up to 6 h with the higher dose ($P < 0.05$) and up to 4 h with the lower dose ($P < 0.05$) of each formulation. There was a significant difference in AUC between 0.2 mg and 0.4 mg of each formulation ($P < 0.05$), the difference between the same dose of both formulations proved not to be significant ($P > 0.05$). FEV_1 increased on all 4 occasions ($P < 0.05$) with mean maximum changes as follows: $30 \pm 1.60\%$ for MDI 0.2 mg and $33 \pm 1.79\%$ for MDI 0.4 mg compared with $27 \pm 1.45\%$ for DPC 0.2 mg and $32 \pm 2.06\%$ for DPC 0.4 mg (Figure 2). There was no difference in AUC. Fenoterol had no significant effect on heart rate; there was no rise in supraventricular or ventricular ectopic beats and no important arrhythmias.

Tremor increased in a dose-dependent manner with MDI only, measurable from 10 min up to 2 h after inhalation (Figure 3). Fenoterol DPC showed no significant increase in tremor amplitude. The mean maximum change in tremor acceleration was $24 \pm 2.03\%$ for MDI 0.2 mg and $49 \pm 2.54\%$ for MDI 0.4 mg compared with $15 \pm 3.17\%$ for DPC 0.2 mg and $15 \pm 3.94\%$ for DPC 0.4 mg. AUC showed a significant difference between MDI 0.4 mg and DPC (both doses) ($P < 0.05$).

The plasma potassium concentration was reduced more by MDI than by DPC, the difference between MDI 0.4 mg compared with the other medications being

Figure 1 Increase in specific airway conductance after single doses of fenoterol: MDI 0.2 mg (■), MDI 0.4 mg (○), DPC 0.2 mg (●), DPC 0.4 mg (▲).

Data are presented as mean $\pm$ s.e. mean ($n = 24$). MDI = metered dose inhaler, DPC = dry powder capsule.

Figure 2 Increase in FEV₁ after single doses of fenoterol: MDI 0.2 mg (■), MDI 0.4 mg (·), DPC 0.2 mg (●), DPC 0.4 mg (▲).

Data are presented as mean $\pm$ s.e. mean ($n = 24$). MDI = metered dose inhaler, DPC = dry powder capsule.

Figure 3 Increase in tremor amplitude after single doses of fenoterol: MDI 0.2 mg (■), MDI 0.4 mg (·), DPC 0.2 mg (●), DPC 0.4 mg (▲).

Data are presented as mean $\pm$ s.e. mean ($n = 24$). MDI = metered dose inhaler, DPC = dry powder capsule.

significant after 15 min ($P < 0.05$). The mean maximum fall was 0.02 ± 0.04 mmol l⁻¹ for MDI 0.2 mg and 0.36 ± 0.03 for MDI 0.4 mg compared with 0.0 ± 0.06 for DPC 0.2 mg and 0.18 ± 0.06 for DPC 0.4 mg.

No subject reported serious adverse effects. Tremor, restlessness and palpitations of mild degree were the symptoms most commonly reported. Fenoterol MDI 0.4 mg caused more subjective side-effects, the differences were not significant ($P > 0.05$).

Study 2 (cumulative doses)

Two subjects completed only 1 study day; subject 6 discontinued after the MDI test day and subject 10 after the DPC test day, both for personal reasons. The data of 12 patients could be analysed (Table 1). All subjects received all five doses of the drug being tested on each study day. No subject reported serious adverse effects. Tremor and palpitations of moderate to severe degree were the symptoms most commonly reported. Fenoterol DPC caused less subjective side-effects, the differences to fenoterol MDI were statistically significant ($P < 0.05$).

Both formulations of fenoterol caused a significant rise in sGaw and FEV₁ with near-maximum changes

after 3 puffs/capsules (Figure 4). Both formulations caused a dose-dependent rise in heart rate (Figure 4). The mean maximum changes in heart rate were 35 ± 3.81 beats min⁻¹ for DPC and 41 ± 2.25 beats min⁻¹ for MDI. The maximum rise in heart rate in any subject was 53 beats min⁻¹ with DPC and 52 beats min⁻¹ with MDI. There was no difference in AUC for lung function parameters and heart rate. There was no rise in ventricular ectopic beats whereas T wave flattening and U waves occurred at the highest dose in nine patients with MDI and in eight patients with DPC.

The plasma potassium concentration was reduced less by DPC than by MDI, the difference being significant from 3 puffs/capsules onwards ($P < 0.05$) (Figure 5). The mean maximum fall was 0.68 ± 0.09 mmol l⁻¹ with DPC compared with 0.96 ± 0.10 for MDI. The maximum fall in plasma potassium with DPC in any subject was 1.4 mmol l⁻¹ with DPC and 1.5 with MDI.

Tremor increased in a dose-dependent manner with both formulations but DPC caused a smaller increase in tremor at each dose ($P < 0.05$) (Figure 5). The mean maximum change in tremor acceleration was 51.58 ± 6.41 cm s⁻² for DPC compared with 95.83 ± 6.75 for MDI. The difference in AUC proved to be significant ($P < 0.05$).

Figure 4 Change in specific airway conductance, FEV_1 and heart rate with cumulative doses of fenoterol DPC ($\blacktriangle$) and fenoterol MDI ($\blacksquare$). Data are presented as mean $\pm$ s.e. mean ($n = 12$). MDI = metered dose inhaler, DPC = dry powder capsule.

Blood pressure changed with both formulations after the highest cumulative dose ($P < 0.05$). The mean maximum increase in systolic blood pressure was 27.09 ± 3.80 mm Hg for DPC compared with 34.16 ± 2.57 mm Hg for MDI. The mean maximum decrease in diastolic blood pressure was 22.5 ± 2.20 mm Hg for DPC compared with 20.00 ± 2.16 for MDI.

Discussion

Dry powder formulations have been developed for nearly all inhalative β_2 -adrenoceptor agonists. Several

Figure 5 Change in plasma potassium and tremor amplitude with cumulative doses of fenoterol DPC ($\blacktriangle$) and fenoterol MDI ($\blacksquare$). Data are presented as mean $\pm$ s.e. mean ($n = 12$). MDI = metered dose inhaler, DPC = dry powder capsule.

clinical trials have shown a comparable bronchodilator effect of dry powder formulations and pressurized aerosols in patients with asthma [14–23]. Other studies suggested a better response with the MDI [24, 25]. Little information has been published on the tremor response, cardiovascular, and hypokalaemic effects of dry powder formulations [26, 27]. We therefore compared bronchodilatation and adverse effects of fenoterol DPC and fenoterol MDI in asthmatics who took conventional low, single doses of both formulations (study 1) and multiples of these doses (study 2). Study 1 was designed to assess the pharmacodynamic profile of fenoterol DPC on lung function, heart rate, tremor and plasma potassium concentration. For study 2, we chose to take repeated measurements at different intervals after inhalation for each variable so that all changes would be near maximum as known from study 1 and other authors [11].

Conventional low doses of fenoterol had no measurable influence on heart rate in our patients. In study 2, multiples of these doses of fenoterol DPC produced a similar increase in heart rate response as provoked by the MDI. The gradients from the steep part of the chronotropic dose-response curve were similar for both formulations. Fenoterol DPC caused substantially less tremorogenic and hypokalaemic effects than the MDI. These differences in tremor response and plasma potassium concentration, found after conventional low

doses, are in accordance with the results of a previous study in asthmatics comparing 0.4 mg fenoterol applied by MDI and by DPC [28] and could also be found with high, cumulative doses of fenoterol in study 2. The separation of the β_2 -mediated systemic effects of tremor and potassium between MDI and DPC emerged at a cumulative dose of 3 puffs/capsules and was still evident at the highest dose. As maximum changes occurred 10 to 20 min after each dose for heart rate, tremor and plasma potassium in all subjects, an underestimation of the maximum changes can be excluded for both formulations of fenoterol. The falls in plasma potassium were accompanied by dose related electrocardiographic effects including T wave flattening and U waves. These ECG changes occurred equally frequently at the highest cumulative dose of both formulations and have been considered a consequence of hypokalaemia [29]. Similar ECG effects have been found with cumulative doses of inhaled salbutamol MDI [30].

The differences in tremor response and plasma potassium concentration may result from a difference in the pharmacokinetic profile of the two formulations of fenoterol, particularly differences in distribution and absorption. Although dry powder formulations of β -adrenoceptor agonists have been used for the management of asthma for more than a decade, very little is known about the amount of drug that is deposited in the airways and the pattern of drug delivery within the body [25].

We found that the degree of bronchodilatation was similar for both formulations. Our results accord with other studies which showed the same bronchodilator capacity of fenoterol DPC and MDI [14,16–19,23,28]. In study 1, the corresponding doses caused an equally effective rise in sGaw; the onset of effect was slightly faster with the MDI whereas the duration of action was longer with the DPC. In study 2, a cumulative dose of 3 puffs/capsules produced lung function responses near the top of the dose-response curve, whereas for β_2 -mediated systemic effects a plateau effect could not be reached even after the highest cumulative dose. These findings are in keeping with the results of other authors [11]. In normal subjects a plateau level of the airways dose-response curves occurred with lower doses of salbutamol than for systemic effects due to exposure of airways β -adrenoceptors to high local concentrations of salbutamol compared with the low plasma levels in the periphery [31, 32]. Similar responses to fenoterol are shown in our asthmatics. The early plateau in airways responses makes it very difficult to compare airways effects and systemic effects at equivalent doses as the systemic curves have not even reached the steep part of the dose-response curve.

It is difficult to examine drug effects in patients with moderate to severe asthma because of inherent variability in airway calibre and concomitant β -adrenoceptor agonist therapy. In asthmatics the bronchodilator action represents the summation of the relaxant effect on the airways and the antagonistic constrictor mechanisms. The systemic effects may be affected by tachyphylaxis due to a down-regulation of the β_2 -receptors [33, 34]. Studies in patients with asthma showed that broncho-

dilator dose-response effects were unaffected by prior treatment with inhaled β_2 -adrenoceptor agonists, but, in contrast, systemic dose-response curves concerning chronotropic and metabolic responses were shifted to the right as a consequence of tachyphylaxis from exogenous β -adrenoceptor agonist therapy [33, 34]. The sparing of airway β_2 -receptors from down-regulation is also supported by *in vitro* studies [35, 36]. The tissue dissociation of β_2 -adrenoceptor agonist induced subsensitivity in asthmatics could not be shown in healthy volunteers who developed a progressive fall in their airway response to inhaled salbutamol while the asthmatic subjects clearly maintained their response [37]. Otherwise, corticosteroid therapy is known to restore lymphocyte β -responsiveness in asthmatic patients taking long-term β -adrenoceptor agonists [38]. All our patients were on regular treatment with inhaled corticosteroids (1000–2000 μ g beclomethasone dipropionate daily) and on regular medication with inhaled β_2 -adrenoceptor agonists (600–1200 μ g salbutamol daily). As our patients had a FEV₁ <60% predicted prior to the start of the study, it was not possible to discontinue the β_2 -adrenoceptor agonists for a washout period necessary to allow reversal of receptor down-regulation which may have affected systemic responses. Therefore the systemic responses for both, the dry powder formulation and the pressurized aerosol, may have been underestimated in our study and would have been shown more clearly in normal subjects who have no tachyphylaxis from previous therapy. In healthy volunteers the wash-out phase between medication periods can be extended as long as necessary to allow reversal of β -adrenoceptor down-regulation.

Conclusion

Single and cumulative doses of fenoterol DPC caused the same bronchodilator but less hypokalaemic effects and less tremor response resulting in attenuation of the subjective feeling of restlessness and finger tremor. Therefore, fenoterol DPC, used in low, therapeutic doses, is preferable to the MDI. Our findings with cumulative doses of fenoterol DPC on heart rate and on plasma potassium as well, are relevant to the changes that might be expected when a patient takes a large dose for deteriorating asthma within a few hours. Patients with severe asthma may be more vulnerable to hypoxaemia and hypokalaemia as a result of previous treatment with β -adrenoceptor agonists, theophylline and other concomitant medications [39]. Therefore, fenoterol DPC, used as rescue medication in high, cumulative doses, do not suggest a greater safety margin and the same restrictions should be considered for the fenoterol dry powder formulation as suggested for the MDI [11].

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