Short-term effects of regular salmeterol treatment on adult cystic fibrosis patients

J. Bargon, K. Viel, N. Dauletbaev, R. Wiewrodt, R. Buhl

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ABSTRACT: Cystic fibrosis (CF) is characterized by chronic lung inflammation leading to airways obstruction. Bronchodilators, particularly short-acting β_2 -agonists, are, therefore, often used by CF patients. The aim of this study was to evaluate, prospectively, the effects of the long-acting β_2 -agonist salmeterol in adult CF patients.

Twenty six patients with CF (10 males and 16 females; mean age ($\pm$ SEM) 28 ± 2 yrs) with mild-to-moderate airways obstruction (baseline forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) $56 \pm 2\%$) were monitored in an open, cross-over trial for 4 weeks by means of peak expiratory flow rates (PEFR), self-recorded symptom scores and body plethysmography. During a 2 week run-in period, all patients continued their treatment, including regular short-acting β_2 -agonists. In weeks 3 and 4, short-acting β_2 -agonists were replaced by the long-acting β_2 -agonist, salmeterol ($50 \mu\text{g b.i.d.}$).

Salmeterol produced a significant increase in PEFR compared to the run-in period (morning 375 ± 23 vs 332 ± 23 L·min⁻¹, Δ PEFR $+15.1 \pm 3.1\%$, $p < 0.003$; evening 384 ± 24 vs 349 ± 24 L·min⁻¹, Δ PEFR $+11.7 \pm 2.4\%$, $p < 0.04$). Similarly, patients reported lower symptom scores, e.g. less dyspnoea during the day, fewer nocturnal awakenings, less intense cough, and fewer unscheduled puffs of short-acting β_2 -agonists.

Thus, the long-acting β_2 -agonist salmeterol provided clinical benefit to a majority of adult cystic fibrosis patients with airways obstruction. These short-term results are promising enough to set up long-term controlled studies.

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Lung disease in patients with cystic fibrosis (CF) is characterized by an inflammatory process centred on the airways, with spreading to the submucosa [1–3]. Epithelial changes are early and include: denudation; impaired mucociliary clearance due to loss of cilia; squamous metaplasia; hypertrophy of mucous glands; and, later, mucopurulent plugging of the airways with acute and chronic inflammatory exudates leading to airways obstruction [4–7]. In addition to chest physiotherapy, bronchodilators, particularly short-acting β_2 -agonists, are routinely prescribed by physicians and well accepted by a great majority of CF patients for relief of bronchoconstriction and to improve expectoration of bronchial secretions [8–11]. This is true despite the fact that the results of several studies focusing on the effect of bronchodilators in CF patients are contradictory [4, 7–9, 11–14].

Compared to the 4–6 h effect duration of short-acting β_2 -agonists, inhaled long-acting β_2 -agonists are characterized by a prolonged bronchodilator action for more than 12 h [15–18], and a prevention of fall in lung function after allergen challenge for more than 30 h [19]. Current recommendations for the treatment of chronic bronchial asthma include the use of inhaled long-acting β_2 -agonists when asthma symptoms are not controlled by a combination of inhaled corticosteroids and short-acting bronchodilators [20–24]. In chronic obstructive

pulmonary disease (COPD), inhaled long-acting β_2 -agonists may produce some symptomatic benefit even in patients with limited reversibility of airways obstruction [25–27]. Surprisingly, however, very little information is available regarding the effects of these drugs on pulmonary function or respiratory symptoms in patients with CF associated obstructive lung disease, especially given the widespread use of short-acting β_2 -agonists in the disease management of these patients.

Thus, the aim of this study was to evaluate, prospectively, the effects of regular therapy with the long-acting β_2 -agonist, salmeterol, on airways obstruction in CF patients. Salmeterol was chosen because it was the only inhaled long-acting drug available in Germany when the trial was started.

Methods

Subjects

Twenty six nonsmoking adult CF patients with obstructive airways disease enrolled at our CF out-patient clinic participated in this open, prospective, nonrandomized, crossover study (10 males and 16 females; mean age ($\pm$ SEM) 28 ± 2 yrs, range 21–58 yrs). In all patients, the diagnosis was confirmed by repeatedly positive sweat tests. Patients were asked to participate if pulmonary

function tests documented an obstructive pattern (forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) $\leq 80\%$). All patients used short-acting β_2 -agonists (salbutamol) regularly either as metered-dose inhalers (MDIs) or by inhalation with a nebulizer (Pari Master or Pari Boy; Pari, Starnberg, Germany) twice daily for at least 1 yr. All patients were well trained in using their MDI or nebulizer, and instructions were repeated once a year by a physiotherapist to avoid sub-optimal treatment. In addition, most patients also used a short acting β_2 -agonist *via* MDI as on-demand medication. The severity of CF lung disease was evaluated on the basis of the latest chest radiograph using the Chrispin-Norman score (pretherapy 12 ± 0.7 , range 5–20) and pulmonary function tests (table 1). All patients attended the clinic regularly and showed no signs of acute infection during the study period.

Study design

During the first 2 weeks (days 1–14) of the 4 week study period, patients continued their regular medication without any change. Starting on day 15, for the following 2 weeks, therapy with regular short-acting β_2 -agonists was replaced by salmeterol, 50 μg given unblinded twice daily *via* an MDI. Patients were asked to use short-acting β_2 -agonists for symptom relief only. All subjects gave informed consent for the study. The study protocol was approved by the Institutional Review Board of Frankfurt University Hospital.

Pulmonary function tests

Pulmonary function tests were performed in a whole-body plethysmograph (Jaeger, Wuerzburg, Germany) before and 15 min after inhalation of 200 μg salbutamol (two puffs) at the beginning (day 1) and at the end of the study (day 28). All tests were carried out between 10.00 and 12.00 h, meeting the guidelines of the European Respiratory Society [28]. The best of three consecutive recordings was used in the analysis. Measurements included FVC, FEV₁, peak expiratory flow (PEF), and airway resistance (R_{aw}). Patients were instructed not to use short-acting bronchodilators for 6 h and long-acting β_2 -agonists for 12 h prior to pulmonary function tests.

Questionnaire and peak flow measurements

Each patient received a peak flow meter with instructions on how to record in diary cards the best of three consecutive determinations of peak expiratory flow rates (PEFRs) before the first use of any bronchodilator in the morning (between 06.00 and 08.00 h) and in the evening (between 19.00 and 21.00 h) [29]. The patients also received a questionnaire for recording symptoms: shortness of breath (0=none, 1/2=on heavy/light exertion, 3=at rest); coughing (0–3 score points); sputum volume (mL, 0–3 score points); number of nocturnal awakenings due to breathlessness; and number of unscheduled puffs of short-acting β_2 -agonist inhaled during the study period [30].

Laboratory analysis

At the beginning and at the end of the study, blood was drawn for laboratory analysis, testing: electrolytes, C-reactive protein, erythrocyte sedimentation rate (ESR), renal function, and haematological parameters.

Statistical analysis

All data are presented as mean $\pm$ SEM. Clinical and functional parameters during therapy with short-acting and long-acting β_2 -agonists were compared using the Wilcoxon signed-rank test. A p-value equal to or less than 0.05 was considered significant.

Results

Pulmonary function parameters

All adult CF patients included in the study showed the typical features of obstructive airways disease (table 1). On day 1, following two puffs of salbutamol (100 μg ·puff⁻¹), FVC ($+5.7 \pm 1.2\%$), FEV₁ ($+7.0 \pm 1.2\%$), FEV₁/FVC ($+0.75 \pm 0.73\%$), and PEF ($+6.6 \pm 3.4\%$) did not change significantly ($p > 0.4$, all comparisons). R_{aw} decreased by $25.2 \pm 2.4\%$ ($p < 0.03$). Specifically, six patients responded to salbutamol with a change of FEV₁ of $\geq 10\%$ ($14.5 \pm 1.5\%$; $p < 0.01$), whilst in 9 and 11 patients changes were 5–10% ($8.6 \pm 0.4\%$; $p = 0.01$) and $\leq 5\%$ ($1.6 \pm 0.5\%$; $p > 0.5$) of baseline, respectively. The addition of salmeterol to the patients' medication did not produce a significant change in FVC, FEV₁, PEF or R_{aw} on day 28 ($p > 0.3$, all comparisons) (table 1). Similarly, the effect of salbutamol on pulmonary function parameters on day 28 was unchanged compared to day 1 ($p > 0.2$, all comparisons).

Peak expiratory flow rates

During the 2 weeks of salmeterol treatment, mean morning and evening PEFRs increased significantly compared to the standard treatment period (mean morning PEFR 375 ± 23 vs 332 ± 23 L·min⁻¹, $\Delta\text{PEFR} +15.1 \pm 3.1\%$, $p < 0.003$; mean evening PEFR 384 ± 24 vs 349 ± 24 L·min⁻¹, $\Delta\text{PEFR} +11.7 \pm 2.4\%$, $p < 0.04$) (figs. 1 and 2). In this regard, the degree of reversibility of airways obstruction by salbutamol predicted the therapeutic response to salmeterol. Patients with an initial FEV₁ response to salbutamol of $\geq 10\%$ showed significant PEFR increases due to salmeterol both in the morning and in the evening ($p < 0.02$, all comparisons); whilst in patients with an initial FEV₁ response to salbutamol of $< 5\%$, PEFR did not differ significantly from the initial values ($p > 0.07$).

Symptomatic parameters

The improvements in PEFRs with salmeterol were associated with significant improvements of symptomatic parameters. The degree of dyspnoea (0.57 ± 0.17 vs 0.99 ± 0.26 ; $p < 0.002$) (fig. 2) and the intensity of cough were lower (1.84 ± 0.17 vs 2.25 ± 0.19 ; $p < 0.03$). Salmeterol

Table 1. — Results of pulmonary function tests of 26 cystic fibrosis (CF) patients before and after a 2 week period of treatment with salmeterol, 50 µg *b.i.d.*

Parameter	Before salmeterol treatment		After salmeterol treatment	
	Baseline	Response to salbutamol	Baseline	Response to salbutamol
FEV ₁ L	1.6±0.1	1.7±0.1	1.6±0.1	1.7±0.1
FEV ₁ % pred	45±4	48±4	46±4	48±4
FVC L	2.9±0.2	3.0±0.2	2.9±0.2	3.0±0.2
FVC % pred	67±4	71±4	69±4	71±4
FEV ₁ /FVC %	56±2	57±2	54±3	55±2
PEF L·s ⁻¹	5.4±0.43	5.7±0.44	5.7±0.4	5.9±0.4
PEF % pred	64±4	72±4	70±4	72±4
R _{aw} cmH ₂ O·L ⁻¹ ·s	5.5±0.8	4.0±0.6	4.9±0.6	4.0±0.5

Tests were always performed before (Baseline) and 15 min after inhalation of 200 µg salbutamol. Data are presented as mean±SEM. FEV₁: forced expiratory volume in one second; % pred: percentage of predicted value; FVC: forced vital capacity; PEF: peak expiratory flow; R_{aw}: airway resistance.

Fig. 1. — Mean morning and evening peak expiratory flow (PEF) rates as percentage of predicted value (% pred) of 26 cystic fibrosis (CF) patients during 2 week periods of regular treatment with salbutamol and salmeterol. Values are presented as mean±SEM. —○—: morning; —●—: evening.

Fig. 2. — Effect of a 2 week period of treatment with salmeterol on peak expiratory flow rates (PEFRs) and symptoms of 26 cystic fibrosis (CF) patients. The data are presented as the percentage change (mean±SEM) from baseline established during a 2 week period of regular therapy with salbutamol.

also improved the quality of sleep (nocturnal awakenings per night 0.13 ± 0.04 vs 0.20 ± 0.06 ; $p < 0.015$). This was paralleled by a decrease in the number of unscheduled puffs of short-acting β_2 -agonists inhaled daily as on-demand medication (0.07 ± 0.04 vs 0.30 ± 0.10 ; $p < 0.001$). Interestingly, dyspnoea improved even in the 11 patients who did not respond to salbutamol with a change of FEV₁ of at least 5% ($p < 0.04$). The symptomatic benefits were unrelated to changes in sputum production or clearance, the volume of expectorated sputum remained unchanged (0.99 ± 0.1 vs 1.08 ± 0.14 ; $p > 0.4$). At the end of the salmeterol treatment period, 24 of 26 CF patients asked for further therapy with long-acting β_2 -agonists, the single most quoted motive being improved exercise capacity.

Safety evaluation

Three patients complained of tachycardia ($n=2$), tremor ($n=1$), and palpitations ($n=1$) during the first study period. All these patients used more than two puffs of salbutamol daily in addition to their regular salbutamol dose ($2 \times 200 \mu\text{g} \cdot \text{day}^{-1}$) when the symptoms occurred. One patient developed a pulmonary exacerbation during week two and had to be hospitalized. The results from this patient were not included in the study. In contrast, no adverse effects were noted during the study period attributable to the administration of salmeterol. Physical examination and all clinical and laboratory parameters remained stable during the salmeterol therapy period ($p > 0.5$, all parameters compared to standard therapy).

Discussion

Therapy of adult CF patients with airways obstruction with the long-acting β_2 -agonist, salmeterol, significantly improved both morning and evening PEFRs and symptomatic parameters. The symptomatic benefit included some of the most frequent pulmonary complaints of adult CF patients, such as dyspnoea following exercise, and quality of sleep. Consequently, 92% of the patients included in this study asked for a continuation of therapy with long-acting β_2 -agonists at the end of the study period.

Obstructive airways disease is frequently seen in a great majority of patients with CF, and inhaled short-acting β_2 -agonists are part of the standard therapy for this disease [7–11]. In a large multicentre trial evaluating the effects of aerosolized recombinant human deoxyribonuclease (rhDNase) on pulmonary function, more than 80% of participating CF patients were treated with bronchodilators [31]. However, there are conflicting reports on the effects of bronchodilating agents on pulmonary function in CF [10, 11, 13, 14], including an increase in airway instability [12]. In a recent double-blind, placebo-controlled study, inhaled salbutamol significantly improved pulmonary function in a majority of hospitalized CF patients [11]. Importantly, a decrease

in pulmonary function overnight was observed, suggesting that longer-acting bronchodilators, such as long-acting β_2 -agonists or theophylline, may be helpful in CF patients. These findings support our hypothesis that long-acting β_2 -agonists may improve control of CF-associated airways obstruction and warrant further study.

In addition, several other factors suggest that this type of therapy could be beneficial for adult CF patients with airways obstruction. Firstly, long-acting β_2 -agonists, such as salmeterol or formoterol, are effective bronchodilators with long duration, a clear advantage compared to short-acting β_2 -agonists [15–19]. This is even more so in advanced airways obstruction, when symptom control by effective bronchodilators is necessary on a regular daily basis rather than on demand [20, 21]. In such settings, addition of long-acting bronchodilators to the therapeutic regimen is clearly superior to increasing the dosage of conventional therapy [22–24]. Theoretically, treatment with short-acting β_2 -agonists *q.i.d.* could have yielded similar subjective and objective results, at least during the day. However, a double-blind 3 month comparison of twice daily inhaled formoterol with inhaled salbutamol *q.i.d.* in patients with asthma demonstrated improved pulmonary function parameters both during the day and overnight, in the formoterol-treated patients [32]. Although the rationale for these recommendations was initially established in patients with bronchial asthma [16–18, 20–24], the results of the present study support the conclusion that long-acting β_2 -agonists may be of similar value in CF patients with airways obstruction. In this regard, a great majority of adult CF patients regularly use β_2 -agonists at least twice daily, and a major complaint of these patients is shortness of breath between inhalations. Thus, many patients have to make frequent use of short-acting β_2 -agonists in addition to their regular twice daily schedule.

The observed lack of increase in FEV₁ contrasts with the increase in PEFR. This is surprising, since there is generally a good correlation between FEV₁ and PEFR. This discrepancy is most likely due to the fact that PEFR measurements were performed in the early morning in the patient's home, whilst pulmonary function tests were carried out between 10.00 and 12.00 h in the hospital. The CF clinic in Frankfurt is a major referral centre for patients with CF, and the limited physical mobility together with the dependency on public transportation of a great majority of patients made it impossible to schedule early hospital tests.

Secondly, as expected, the PEFR response of CF patients to salmeterol was largely dependent on the reversibility of airways obstruction. However, an unexpected result of this study was the fact that some form of clinical benefit due to salmeterol was seen in 93% of patients, rather independent of the degree of reversibility of airways obstruction. In this regard, the prolonged activation of β_2 -adrenoceptors in CF airways may not only provide prolonged bronchodilatation, but also lasting stimulation of ciliary function, another potential benefit in CF patients [33]. There is some similarity to the situation in patients with COPD. In COPD, salmeterol produced symptomatic relief and an improvement in quality of life, but only marginal effects on pulmonary function [25–27]. In the present study, a

great majority of CF patients asked for further therapy with long-acting β_2 -agonists, mostly due to improved exercise capacity. These results provide further evidence that bronchodilation is not the only mode of action of long-acting β_2 -agonists.

Thirdly, the incidence of adverse effects reported to be attributable to salmeterol was surprisingly low, even given the small number of patients. In patients with asthma, side-effects of salmeterol and salbutamol are comparable in quality and quantity [34]. However, CF patients are familiar with this type of drug and the potential side-effects since early childhood, and may, therefore, be more likely to accept typical adverse effects as "normal".

Finally, the extent of obstructive airways disease in adults with CF is a key parameter of overall quality of life. Typical variables of quality of life in these patients, such as energy, pain, emotion, sleep, social isolation and physical mobility, show a highly significant correlation to measures of airways obstruction, such as FEV₁ [35]. This strong correlation is notable because it is often not seen in other conditions, such as chronic bronchitis and emphysema.

A major concern regarding the chronic, regular use of β_2 -agonists in patients with bronchial asthma is the potential development of tolerance against their effects, particularly on unspecific bronchial hyperresponsiveness, and even the induction of airway inflammation [36–39]. The 2 week treatment period in this study was too short to address these questions. From a theoretical point of view, it is unclear whether these considerations are valid in CF, given the pronounced differences between the chronic neutrophil-dominated inflammatory process in the CF lung [1–3] and the chronic eosinophilic airways inflammation seen in bronchial asthma [20, 21]. Nevertheless, bronchodilator therapy may impair lung function of CF patients [10–14]. It is, therefore, mandatory to monitor the effects both of short-acting and long-acting β_2 -agonists on pulmonary function of each individual patient carefully, to recognize any such effects early, and to discontinue therapy if necessary. This is true despite the fact that salmeterol significantly decreased the number of puffs of short-acting β_2 -agonists used as on-demand medication.

Long-acting β_2 -agonists are not licensed for use in cystic fibrosis patients, and there are no documented clinical experiences with these drugs in this disease. Therefore, this open, nonrandomized, crossover study represents only a first step in the evaluation of long-acting β_2 -agonists as a potential therapy for cystic fibrosis-associated obstructive lung disease. It showed, prospectively, the feasibility, efficacy, and safety of the use of long-acting β_2 -agonists (50 μ g salmeterol inhaled twice daily) in controlling bronchoconstriction and improving pulmonary symptoms when compared with the standard therapy with short-acting β_2 -agonists. However, the message of this study is limited by its design, in particular the lack of blindness, potentially leading to placebo effects. Despite this, the results of this study demonstrate that long-acting β_2 -agonists may be a valuable addition to the therapy of cystic fibrosis patients with obstructive lung disease, and that this type of drug is promising enough to justify long-term controlled studies in patients with cystic fibrosis.

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