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Bronchodilatory Effects of Salbutamol, Ipratropium Bromide, and Their Combination: Double-Blind, Placebo-Controlled Crossover Study in Cystic Fibrosis

Rita Ziebach, MD,[1]* Barbara Pietsch-Breitfeld, MD,[2] Matthias Bichler, MD,[1] Andreas Busch, MD,[1] Joachim Riethmüller, MD,[1] and Martin Stern, MD[1]

Summary. The efficacy of inhaled sympathomimetic and anticholinergic agents on airway obstruction in cystic fibrosis (CF) has been proven in several studies. However, studies comparing combined therapy with monotherapy led to divergent results, probably due to different study designs, different dosages, and the small numbers of patients investigated. Therefore, we wanted to answer the question which inhalation has the best short term effect: a sympathomimetic or an anticholinergic agent, or the combination of both. We investigated 17 patients with CF on 4 successive days in the morning, using pulmonary function testing before and 30 min after inhalation. Each patient received aerosolized salbutamol (SB, maximum dose (max.) 2.5 mg), ipratropium bromide (IB, max. 0.5 mg), the combination of both, or placebo (normal saline) in a randomized, double-blind crossover design.

The mean forced expiratory volume in the first second improved significantly (adjusted *P*-value < 0.017) after each treatment compared to placebo. Analysis of variance showed that SB and combination therapy with SB and IB were superior to IB alone, without significant difference between SB and combination therapy. Response of a patient to combined therapy was usually associated with response to SB. Long-term efficacy and side effects of treatment with bronchodilators still remain to be investigated after this short term study.

We conclude that in CF patients bronchodilator therapy with sympathomimetic agents is usually sufficient. Only in cases with proven additional benefit from inhalation by anticholinergics should combination therapy be recommended. **Pediatr Pulmonol. 2001; 31:431–435.**

Key words: cystic fibrosis; bronchodilators; pulmonary function testing; ipratropium; albuterol.

INTRODUCTION

The efficacy of bronchodilators on airflow limitation in cystic fibrosis (CF) has been examined in numerous studies,[1–3] as reviewed by Cropp.[4] It was concluded that "most CF patients are likely to benefit from bronchodilator therapy when given in adequate doses, appropriate combinations and by the appropriate route." However, there is still controversy as to whether sympathomimetics or anticholinergics, or their combination, are the best choice for therapy. The effect of high-dose ipratropium bromide (IB), especially in combination with β_2-agonists, remains to be investigated.

Weintraub and Eschenbacher[5] found significant responses in forced expiratory volume in 1 sec (FEV_1) after metaproterenol (1,500 μg), IB (40 μg), and combined therapy, but no significant differences between the trials in 10 adults with CF (average FEV_1 increase from baseline 12.5% after metaproterenol, 17.1% after IB, and 16.6% after a combination of the medications). Sanchez et al.[6] showed a better response to combined therapy (+17% FEV_1) compared to either 5,000 μg albuterol (+8% FEV_1) or 250 μg IB alone (+11% FEV_1) in 9 patients with previously proven responsiveness to bronchodilators (children and adults). In a follow-up study of 9 CF patients, Sanchez et al.[7] showed a similar acute bronchodilator effect of salbutamol (SB, +13.9% FEV_1) and IB (+13.2% FEV_1) when large doses were used. There was no additive effect of combined therapy. Investigations by Kattan et al.[2] and van Haren et al.[3] showed slightly better effects of sympathomimetics compared to anticholinergics on airway obstruction in CF patients. In both studies, the medications were not

[1]University Children's. Hospital Tübingen, Department 1, Tübingen, Germany.

[2]Institute for Medical Informatics, University of Tübingen, Tübingen, Germany.

*Correspondence to: Dr. Rita Ziebach, University Children's Hospital, Hoppe-Seyler-Straße 1, 72076 Tübingen, Germany.
E-mail: rita.ziebach@med.uni-tuebingen.de

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combined. Eber et al.[1] combined oral theophylline with inhaled SB and found that combination therapy was not superior to SB alone, and could even lead to expiratory airway compression in some patients.

Based on these data, no recommendation can be made about the best choice for short-term bronchodilator therapy in CF. We therefore studied the effects of IB and SB alone and in combination on lung function in CF.

MATERIALS AND METHODS

All patients at our CF center over 6 years of age who were able to perform pulmonary function tests (PFT) reproducibly were asked to take part in this study. Seventeen out of 60 patients and their parents agreed to participate and gave informed consent. All participants were in stable condition, without clinical signs of acute airway infection. Patients on steroids or methylxanthines were excluded from the study.

Most eligible patients who refused participation did not tolerate the considerable time required for coming to the hospital on 4 successive days. Seven in-patients were investigated at the end of a 14-day course of i.v. antibiotics given routinely every 3 months without prior pulmonary deterioration. There was no preselection of patients for bronchial hyperreactivity or for known bronchodilator responsiveness. Approval of the local ethics committee was obtained.

Measurements of spirometry and body plethysmography (MasterLab® equipment, Jaeger, Wüerzburg, Germany) were performed before and 30 min after bronchodilator inhalation. During this time, patients did not receive chest physiotherapy or engage in physical activity. Testing was done by one technician and by one physician for the duration of the trial. In order to achieve maximal standardization of PFT, each patient was evaluated at the same time of day, between 9–12 AM on 4 successive days. The last inhalation of bronchodilators prior to PFT was at least 12 hr earlier (washout). Patients were randomized to be treated on 4 successive days with drugs or placebo as follows: SB + IB, SB alone, IB alone, or placebo (normal saline). Dosages were as follows: SB 250 μg/year of age up to 2,500 μg, and IB 50 μg/year of age up to 500 μg. Normal saline (2 mL) was added to the medications. The dosage schedule was chosen according to common practices in the treatment of pediatric asthma. Inhalation was performed with a compression nebulizer (Pari Master/Parill® nebulizer with mouthpiece, Pari, Starnberg, Germany). With this equipment the median mass diameter of the inhaled particles was 3.6 μm, 65% <5 μm with an output of 480 mg/min.

Medications were prepared by a person not involved in the measurements, so that investigators and patients were blinded. The random code was issued independently by the Institute for Medical Informatics, University of Tübingen. Statistical analysis of the results for FEV_1, forced vital capacity (FVC), and forced expiratory flow at 25–75% of vital capacity (FEF_{25-75}) was performed by analysis of variance, designed for crossover studies (carry-over effect, medication effect, learning effect).[8] Using three main outcome criteria (FEV_1, FVC, and FEF_{25-75}), analysis of variance was performed on the adjusted significance level of $P < 0.017$ (Bonferroni adjustment).[9] A positive bronchodilator response was defined according to Ries:[10] improvement ((post-pre) $\times$ 100/pre (%)) for FEV_1 of at least 15%, and for FEF_{25-75} of at least 20%.

ABBREVIATIONS

BMI	Body mass index
CF	Cystic fibrosis
FEV_1	Forced expiratory volume in first second
FVC	Forced vital capacity
FEF_{25}	Forced expiratory flow at 25% of vital capacity
FEF_{25-75}	Forced expiratory flow at 25–75% of vital capacity
IB	Ipratropium bromide
PFT	Pulmonary function testing
Raw	Airway resistance
SB	Salbutamol (albuterol)
SEM	Standard error of the mean
TGV	Thoracic gas volume
WFH	Weight for height

RESULTS

Seventeen patients entered our study (patient characteristics in Table 1). Most of them (n = 12) had normal lung function. One girl (number 17) dropped out after 2 days because of an acute gastrointestinal infection. Her study data were included in the statistical analysis.

Since there was no significant difference in baseline FEV_1, FEF_{25-75}, and FVC between the four trials of each patient, carry-over and learning effects were ruled out. Analysis of variance showed the effect of all drugs vs. placebo ($P = 0.0001$), and of each drug by comparison between placebo and the three medications. Mean increase of FEV_1 from baseline was 7% ($\pm$ 0.4% standard error of the mean (SEM)) after SB, 6% ($\pm$ 0.5% SEM) after IB, and 8% ($\pm$ 0.4% SEM) after combined medication. A mean decline in FEV_1 of 1% ($\pm$ 0.3% SEM) occurred after placebo. Mean changes of FEF_{25-75}, and FVC are shown in Figure 1 and Table 2.

FEV_1, FEF_{25-75}, and FVC improved significantly after SB and after combination therapy, compared to placebo. After IB, FVC did not change significantly in comparison with placebo, whereas FEV_1 and FEF_{25-75} improved significantly ($P = 0.0045$ respiration $P = 0.0001$). IB alone tended to be less effective than IB in improving FEV_1 and FVC, compared to SB and combination therapy; the differences were not statistically significant ($P = 0.2116$, resp. $P = 0.1702$ for FEV_1, $P = 0.0539$, resp. $P = 0.0922$ for FVC).

TABLE 1—Patient Characteristics

Patient	Age (years)	Nutritional status[1]		Gender	Baseline FEV_1	
		BMI	WFH		L	%[2]
1	16	—	102	f	3.76	120.3
2[3]	15	—	88	f	2.35	92.0
3[3]	14	—	110	f	1.87	76.0
4[3]	19	18.0	—	f	1.80	58.8
5	33	20.0	—	f	1.53	48.5
6	9	—	94	m	1.82	89.0
7	9	—	103	m	1.54	109.5
8	7	—	98	f	1.33	99.8
9[3]	13	—	100	f	2.21	93.3
10[3]	12	—	119	m	2.63	126.5
11[3]	18	22.2	—	m	3.01	73.3
12[3]	10	—	106	f	1.77	105.5
13	9	—	117	f	2.39	128.8
14	25	27.4	—	m	4.00	95.0
15	29	21.7	—	m	2.66	72.3
16	7	—	92	f	1.71	101.5
17	10	—	92	f	2.03	83.5

[1]Nutritional status is expressed as body mass index (BMI) for adult patients, and as weight for height (WFH) for patients up to 18 years of age. WFH: (Weight/WFH optimum) 100 (%), normal values.[18]
[2]FEV_1 (% of predicted): normal values.[19,20]
[3]Patients at end of a routine i.v. course of antibiotics.

Airway resistance (Raw) and forced expiratory flow at 25% of vital capacity (FEF_{25}) were not evaluated by analysis of variance. To give an overview, average changes of these parameters are shown in Table 2 and Figure 1.

Three of the 17 patients exhibited responses of $FEV_1 \geq 15\%$ for combination therapy. One of them responded to SB and to IB, one showed response to SB. Two patients responded to SB, but not to combination therapy or to IB (Fig. 2). The influence of bronchodilators on the small airways was impressive (Fig. 3): improvement of $FEF_{25-75} > 20\%$ was shown in 12 patients. Seven of these patients were responders to combination therapy. Response to combination therapy was always associated with response to either SB ($n = 2$), IB ($n = 1$), or both ($n = 4$). Decrease in FEF_{25-75} occurred in patient number 10 after IB and in patient number 8 after normal saline.

No side effects were experienced by the patients. FEF_{25} did not decrease after bronchodilator inhalation in our patients except for patient number 10 after IB.

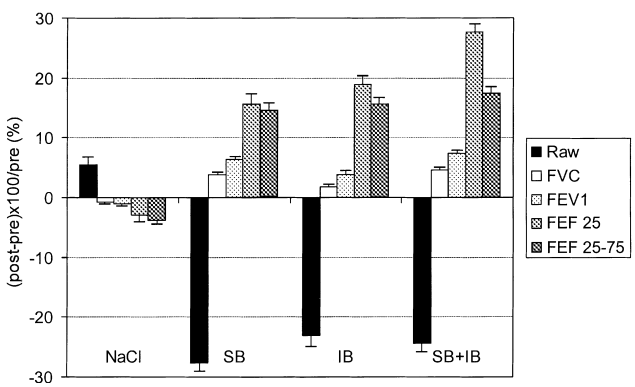

Fig. 1. Mean relative changes of PFT parameters. Mean relative changes and SEM of PFT parameters after normal saline, SB, IB, and SB + IB.

DISCUSSION

This study was performed to investigate the bronchodilator effects of combined SB and IB in CF patients compared to monotherapy. Our patients showed similar response to SB combined with IB compared to SB alone. Response to IB alone tended to be inferior to response to SB alone. The three parameters analysed (FEV_1, FVC, and FEF_{25-75}) were chosen in order to make the results comparable to previous studies.[1–3,5,6,11,12]

In comparison with our data, two previous studies led to divergent results: Sanchez et al.[6] did not show an advantage of combination therapy, while Weintraub and Eschenbacher[5] found a better response to combination therapy compared to albuterol or IB alone. The outcome of these three studies was probably influenced by differences in study design (no placebo in Sanchez et al.,[6] and different dosages, patient age, and baseline lung function) as well as by preselection of patients, by different timing with regard to daytime, and by different sample sizes.

The study design of Weintraub and Eschenbacher[5] was double-blind, placebo-controlled. Statistical analysis was performed by two-way analysis of variance with a $P = 0.05$ level evaluating changes of FEV_1.[5] Time interval between the four trials was at least 12 hr. The

TABLE 2—PFT at Baseline and 30 Min After Inhalation of SB, IB, or SB + IB[1]

	SB		IB		SB + IB	
	Baseline	Final	Baseline	Final	Baseline	Final
Raw (cmH_2O/L/sec)	0.46 ± 0.02	0.34 ± 0.01	0.50 ± 0.01	0.39 ± 0.01	0.47 ± 0.01	0.35 ± 0.01
TGV (L)[2]	2.13 ± 0.06	2.16 ± 0.06	2.20 ± 0.06	2.10 ± 0.07	2.23 ± 0.05	2.16 ± 0.05
FVC (L)	2.83 ± 0.05	2.95 ± 0.06	2.84 ± 0.06	2.90 ± 0.06	2.80 ± 0.56	2.94 ± 0.56
FEV_1 (L)	2.26 ± 0.04	2.41 ± 0.05	2.26 ± 0.05	2.43 ± 0.05	2.22 ± 0.05	2.38 ± 0.06
FEV_1/FVC (%)	80.5 ± 0.66	82.5 ± 0.59	79.9 ± 0.71	81.5 ± 0.62	79.5 ± 0.62	81.9 ± 0.63
FEF_{25} (L/sec)	1.07 ± 0.04	1.26 ± 0.05	1.02 ± 0.05	1.20 ± 0.05	0.96 ± 0.04	1.20 ± 0.05
FEF_{25-75} (L/sec)	2.18 ± 0.07	2.55 ± 0.08	2.14 ± 0.08	2.48 ± 0.09	2.13 ± 0.07	2.47 ± 0.08

[1]Values are means ± SEM.
[2]Thoracic gas volume (TGV) measured by body plethysmography.

maximal interval was not mentioned. The influence of time of day on bronchial responsiveness and intraindividual variability of longitudinal responses to bronchodilators were not taken into account.[11,12]

The study design of Sanchez et al.[6] was double-blind, randomized, and crossover without placebo control, using statistical analyses (*t*-tests, analysis of variance) with a $P = 0.05$ level evaluating six different parameters. The use of multiple statistical tests without adjustment of *P*-values[9] and of several tests on the same data increases the risk of statistical misinterpretation. The three trials were performed for each patient at the same time of day during a 2-week period.

Hordvik et al.[11] showed a significantly reduced response to bronchodilators in the afternoon compared to the morning. This was probably due to multiple therapeutic effects, including chest physiotherapy carried out in the morning. However, it is well-known that bronchial reactivity and lung function change with daytime in asthmatic and even healthy individuals.[13,14] Chronic infection of the lung also influences bronchodilator responses significantly: Hordvik et al.[15] found a much better response after 1 week of i.v. antibiotic treatment in a study looking at this confounding factor. Thus, reliable testing of bronchodilator effects in CF patients has to be performed at the same time of day and at the same place in the individual daily therapeutic schedule (in particular regarding chest physiotherapy). Tests should be done within a short period, e.g., for short-acting substances like SB and IB within 4 days at the end of a routine i.v. treatment or when subjects are clinically stable.

Our sample size was larger compared to the studies cited. Looking at the characteristics of our patients, they were younger and their baseline PFTs were better compared to the patients of Weintraub and Eschenbacher.[5] Baseline PFTs of the pediatric and adult patients in Sanchez et al.[6] were shown as absolute values, and therefore were not comparable to other data.

The dose of IB was higher in the present than in the previous study. In our study and in the studies cited, standard doses and standard nebulizers or metered dose inhalers recommended for routine therapy in asthmatic patients were used. The same was true for the β_2-agonist dose, which was highest in Sanchez et al.[6] Inhalation was performed with a face mask in the patients of Sanchez et al.,[6] which leads to less bronchial deposition than with

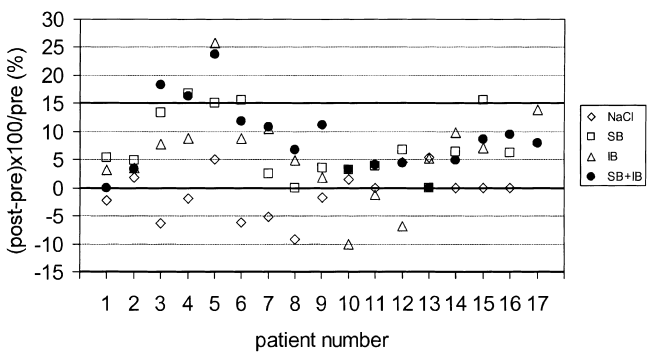

Fig. 2. Relative changes of FEV_1. Individual relative changes of FEV_1 after normal saline, SB, IB, and SB + IB.

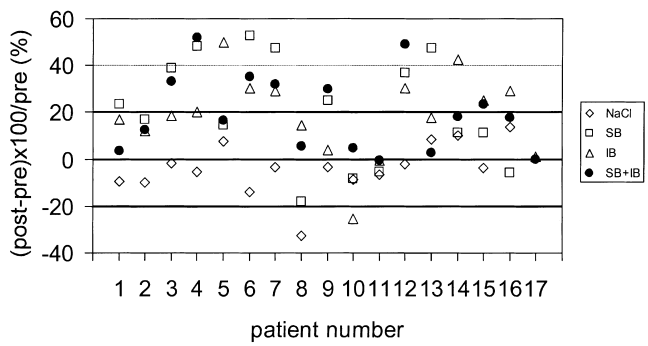

Fig. 3. Relative changes of FEF_{25-75}. Individual relative changes of FEF_{25-75} after normal saline, SB, IB, and SB + IB.

the metered dose inhalers which were used in Weintraub and Eschenbacher,[5] or with nebulization using a mouthpiece, as was done in our patients.[16]

Sanchez et al. [6] focused their analysis and conclusions on patients with a known positive bronchodilator response. Because of this selection bias, his conclusions were hardly comparable to those in other studies. The observation of other investigators,[4] that young patients with good lung function benefit most from bronchodilators, could not be confirmed by our study. However, our data are of limited value in regard to this issue, as only two of our patients had severe deterioration of lung function.

In our patient group there was no significant advantage combining IB with SB compared with SB alone, although IB was given in higher doses than in previous studies. Looking at individual patients, only a few showed any benefit from IB in addition to SB. Based on this experience, we conclude that therapy with short-acting bronchodilators should be established after individual testing. This is recommended not only to prove efficacy, but also to detect any possible unfavorable effect.[17] Routinely, in children and adults with CF, a β_2-agonist should be chosen routinely for bronchodilation. After this short-term study, the long-term efficacy of bronchodilators in CF remains to be evaluated.

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