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Efficacy and Safety of Ipratropium Bromide Plus Fenoterol Inhaled Via Respimat® Soft Mist™ Inhaler vs. a Conventional Metered Dose Inhaler Plus Spacer in Children With Asthma

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Summary. The objective of this study was to compare the efficacy and safety of ipratropium bromide/fenoterol hydrobromide (IB/FEN; Berodual®) delivered from the novel propellant-free Respimat® Soft Mist™ Inhaler (SMI) with that from a chlorofluorocarbon (CFC) metered-dose inhaler (MDI) plus spacer in children with asthma. The study followed a multicenter, randomized, double-blind (within Respimat® SMI), parallel-group design. During the 2-week run-in period, patients received two actuations of CFC-MDI tid (IB 20 μg/FEN 50 μg per actuation) via a spacer (Aerochamber®) (MDI 40/100). Patients (n = 535) were then randomized to: Respimat® SMI containing IB 10 μg/FEN 25 μg (Respimat® SMI 10/25), IB 20 μg/FEN 50 μg (Respimat® SMI 20/50), one actuation tid or CFC-MDI containing IB 20 μg/FEN 50 μg per actuation (in total 1B 40 μg/FEN 100 μg), or two actuations tid via Aerochamber® (MDI 40/100), for 4 weeks. The primary endpoint was the change in forced expiratory volume in 1 second (FEV_1) during the first 60 min after dosing (area under the curve from 0–1 h [$AUC_{0-1\ h}$]) on day 29. Analysis of the primary endpoint demonstrated that the efficacy of Respimat® SMI 10/25 and 20/50 was equivalent to or greater than that of MDI 40/100. Similar results indicating that Respimat® SMI 10/25 and 20/50 were not inferior to MDI 40/100 were also found on days 1 and 15. Analyses of other secondary endpoints supported these results. The safety profile of Respimat® SMI was comparable to that of the CFC-MDI plus spacer. In conclusion, IB/FEN delivered via Respimat® SMI is at least as effective as, and is as safe as, when delivered via CFC-MDI plus Aerochamber® in children with asthma. Use of Respimat® SMI thus enables a 2–4-fold reduction in the nominal dose of IB/FEN, and obviates the need for a spacer. **Pediatr Pulmonol. 2004; 37:264–272.** © 2004 Wiley-Liss, Inc.

Key words: childhood asthma; bronchodilators; fenoterol; ipratropium; Respimat; soft mist inhaler.

INTRODUCTION

The prevalence of asthma appears to be increasing globally, especially in children. In the USA alone, the prevalence of asthma increased by 75% between 1980–1994, with the most substantial increases occurring in the 0–4 and 5–14-year-old groups (increases of 160% and 74%, respectively).[1] Moreover, asthma appears to be the most common chronic disease in children.[2]

Since direct delivery to the lungs enables lower doses to be used, provides more rapid onset of action, and reduces adverse events (AEs), inhalation is the preferred route for

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the administration of drugs used in the management of respiratory disease.[3,4] The combination of ipratropium bromide (IB) and fenoterol hydrobromide (FEN) (IB/FEN; Berodual®) administered by chlorofluorocarbon metered dose inhaler (CFC-MDI), in some cases with a spacer, has been used to treat both adults[5,6] and children with asthma.[7–9]

Metered-dose inhalers (MDIs) are still the most commonly used devices for inhaled administration of bronchodilators for the treatment of asthma. Although MDIs are easy to use in theory, a relatively large proportion of patients, particularly children, have trouble using them in practice. A study conducted in asthmatic children who were using MDIs showed that only 46% of them had an efficient inhaler technique.[10] The need for good coordination to obtain a satisfactory lung dose restricts the use of MDIs in children.[11] The failure to respond to inhaled therapy in early childhood asthma may be attributable to failure of drug delivery.[12]

The Respimat® Soft Mist™ Inhaler (SMI) is a novel multidose inhaler (Fig. 1) with a unique delivery mechanism that uses the energy released from a tensioned spring to force a predefined metered volume of drug solution through the uniblock, a nozzle fed by a set of extremely fine channels. This produces a very fine aerosol for inhalation (the Soft Mist™) without the need for chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellants. These components are illustrated in Figure 2. The Respimat® SMI is easy to use, with the patient simply having to twist the base of the device 180°, press the dose-release button, and inhale the Soft Mist™. To ensure that all the emitted dose is inhaled, patients should inhale for at least 1.5 sec after pressing the dose-release button, and ideally for 2–3 sec. The medication is provided as a solution in a cartridge that is inserted into the device before first use, each cartridge containing 120 actuations. The Respimat® SMI generates a slow-moving cloud with a high fine-particle fraction.[13–15] These characteristics, together with a relatively long duration of dose release (approximately 1.2 sec), significantly reduce oropharyngeal and increase lung deposition

Fig. 1. Respimat® Soft Mist™ Inhaler.

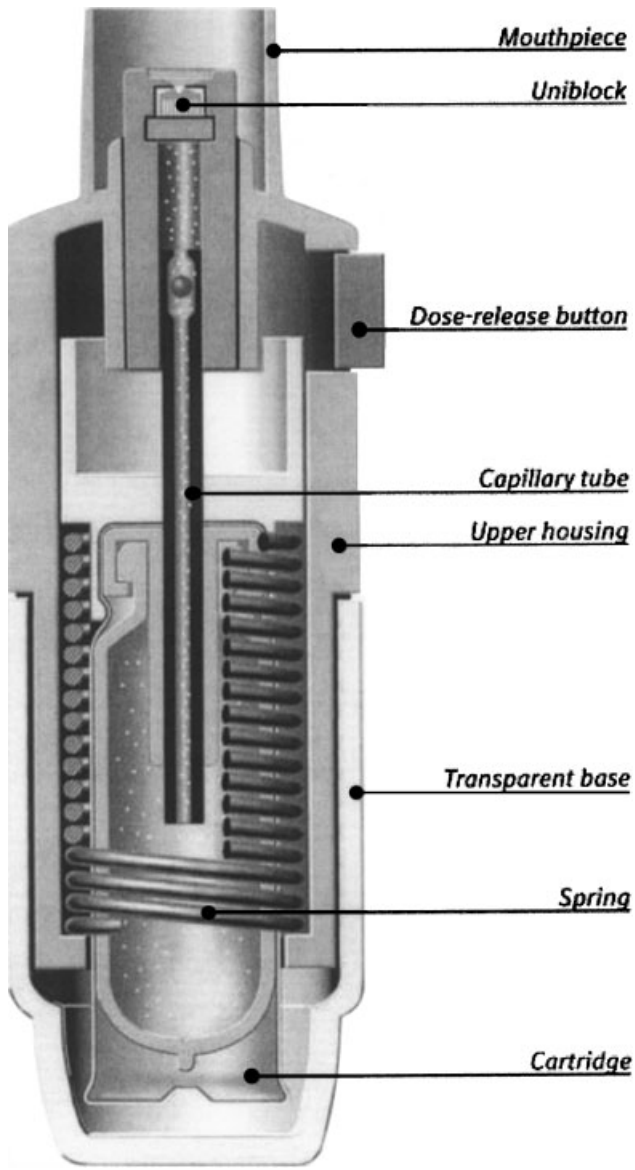

Fig. 2. Sectional diagram of Respimat® Soft Mist™ Inhaler, showing main components of device.

compared with CFC-MDIs and HFA-MDIs.[13–19] The need for hand-lung coordination is also reduced.[14]

The objective of this 4-week study was to compare the bronchodilator activity and safety profile of IB/FEN (10/25 μg or 20/50 μg) delivered as one actuation tid from a Respimat® SMI with those of IB/FEN 40/100 μg delivered as two actuations tid from a CFC-MDI plus spacer in children with asthma. The choice of smaller dosages for the two Respimat® SMI groups was based on the results of a dose-ranging study[20] and a cumulative dose-response study[21] in asthma patients: these showed the bronchodilatory effects of IB/FEN via Respimat® SMI to be equivalent to those via CFC-MDI, when the dosages via Respimat® SMI were one quarter and one half of that given via CFC-MDI.

PATIENTS AND METHODS

Patients

Patients aged 6–15 years with a diagnosis of bronchial asthma were eligible for the study if they had a forced expiratory volume in 1 sec (FEV_1) of 60–90% of predicted normal value[22] and reversible airway obstruction (FEV_1 increase $\geq$12% over baseline 30–60 min after two actuations of IB/FEN (Berodual®) CFC-MDI used with an Aerochamber®). Patients were also required not to have been hospitalized for an exacerbation and to have had a stable dosage of pulmonary medication in the 4 weeks before the study.

Exclusion criteria included: a history of clinically significant diseases other than bronchial asthma; severe asthma with frequent nocturnal attacks or frequent exacerbations; and upper or lower respiratory tract infection during the 4 weeks before run-in. Girls having had their menarche who were sexually active or not using approved contraceptive methods were excluded.

The use of β-adrenergic and anticholinergic bronchodilators (short- and long-acting), oral corticosteroids, leukotriene receptor antagonists, and 5-lipoxygenase inhibitors was not allowed during the study. Concomitant medications that were allowed included: stable doses of inhaled corticosteroids, inhaled sodium cromoglycate and nedocromil, and oral xanthines. Appropriate washout periods for bronchodilators were used before pulmonary function tests.

Study Design

This multicenter, randomized, double-blind (within Respimat® SMI), active-controlled, parallel-group study was conducted in 54 centers in four countries between September 1998–July 1999. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The local Ethics Committee or Institutional Review Board of each center approved the study protocol. Written informed consent was obtained from the child's parents or legally authorized representative. If possible, informed consent was also obtained from the child.

During the 2-week run-in period, all patients received two actuations of IB/FEN CFC-MDI tid (IB 20 μg/FEN 50 μg per actuation) via an Aerochamber®. Children who developed an upper or lower respiratory tract infection or who required the use of oral steroids during run-in were excluded from randomization. The remaining patients were randomized (in a 1:1:1 ratio) to one of three treatments for 4 weeks:

- Respimat® SMI IB 10 μg/FEN 25 μg, one actuation tid (Respimat® SMI 10/25);
- Respimat® SMI IB 20 μg/FEN 50 μg, one actuation tid (Respimat® SMI 20/50); or
- CFC-MDI IB 20 μg/FEN 50 μg per actuation, two actuations tid administered via Aerochamber® (MDI 40/100).

Treatment was open-label for devices and double-blind only for the IB/FEN dose delivered by Respimat® SMI. A double-dummy design was not used, because inhalation of excipients from both devices would have made it impossible to assess any switch effect or the incidence of AEs caused by excipients of either device. Salbutamol CFC-MDI 100 μg per actuation prn (via Aerochamber®) was used as rescue medication.

Assessments

Schedule of Assessments

There were 4 clinic visits: an initial screening visit (visit 1) followed by a 2-week run in, and then visits 2–4 on days 1, 15, and 29 of the treatment period. At visit 1, demographic data were recorded, and patients provided a medical history and underwent both physical examination (including blood pressure and pulse rate) and pulmonary function tests (baseline FEV_1 and forced vital capacity (FVC), and testing for FEV_1 reversibility). At visits 2–4, FEV_1, forced midexpiratory flow ($FEF_{25-75\%}$),[23] FVC, pulse rate, and blood pressure were recorded predose and 5, 30, and 60 min postdose; daily diary recordings for morning and evening predose peak expiratory flow rate (PEFR) and number of daily actuations of study and rescue medication were also reviewed. Physical examination was repeated on day 29.

To minimize the influence of diurnal pulmonary variation, the start time of pulmonary function testing at visits 3 and 4 had to be within 30 min of that at visit 2.

Efficacy

The primary endpoint was the change from predose in FEV_1 in the first 60 min after dosing, calculated as area

under the FEV_1-time curve between 0–1 hr ($AUC_{0-1\ h}$) on day 29.

Secondary efficacy endpoints were: change from predose in FEV_1 ($AUC_{0-1\,h}$) on days 1 and 15; total FEV_1 calculated as AUC between 0–1 hr ($TAUC_{0-1\,h}$) on day 29; peak FEV_1 achieved in the first 60 min after dosing on days 1 and 29 (measured as change from predose value); FVC on all test days (days 1, 15, and 29); $FEF_{25-75\%}$ on all test days; and weekly mean values of a) predose morning and evening PEFR and b) total daily inhaled rescue medication.

Safety

The safety of the study treatments was assessed by monitoring the incidence of adverse events throughout the treatment period and by measuring blood pressure and pulse rate on test days. Patients also had a physical examination at screening and at the end of the study.

The effect of switching from CFC-MDI to Respimat® SMI was assessed by comparing morning and evening PEFR, rescue medication use, and respiratory AEs in the first 2 weeks of randomized treatment with the corresponding values during the 2-week run-in.

Statistical Analysis

The primary study objective was to demonstrate that at least one of the two doses of IB/FEN via Respimat® SMI produced a bronchodilator response that was noninferior to (i.e., equivalent to or better than) that obtained from IB/FEN via CFC-MDI. The null hypothesis was that each IB/FEN dose delivered via Respimat® SMI is therapeutically inferior to that delivered via CFC-MDI by at least 0.075 l in the change from predose in FEV_1 during the first 60 min after dosing ($AUC_{0-1\ h}$) after 4 weeks' treatment. Noninferiority was determined by examining the 95% confidence intervals (CIs) for the adjusted mean difference between each dose from the Respimat® SMI and CFC-MDI, accompanied by a test of whether the difference between pairs of treatments (IB/FEN Respimat® SMI − IB/FEN CFC-MDI) lay in the therapeutically inferior region ($-\infty$ to -0.075 l). A stepwise procedure first examined the difference between Respimat® SMI 20/50 and MDI 40/100. Only if this Respimat® SMI dose was not inferior to the MDI was Respimat® SMI 10/25 to be compared with the MDI in the second step. Testing Respimat® SMI 20/50 first was necessary to maintain overall one-sided type I error at $\alpha = 0.025$.

A sample size of 135 patients per treatment group (total, 405 patients) was needed to conclude that neither IB/FEN dose delivered via the Respimat® SMI was inferior to IB/FEN delivered via the CFC-MDI at a 2.5% level of significance with a power of approximately 80%, given that the formulations were equal.

The primary endpoint was evaluated by analysis of covariance (ANCOVA), including country and treatment with baseline on day 1 (visit 2) as covariate. Analyses of secondary endpoints were explanatory.

Primary and secondary efficacy analyses of all spirometry data were performed on the clinic spirometry per-protocol (PP) population and confirmatory analyses done on the clinic spirometry intention-to-treat (ITT) population; analyses of morning and evening PEFR were done in distinct PP populations; definitions of all these populations are given in Table 1. All randomized patients (safety population) were included in the AE summaries.

RESULTS

Patients

The breakdown of patient populations by treatment group is shown in Table 1. In total, 691 patients were enrolled, of whom 156 were not randomized (primarily because of failure to fulfill inclusion/exclusion criteria), leaving 535 patients who were randomized to treatment

TABLE 1—Patient Disposition[1]

Population	Respimat® SMI 10/25 μg	Respimat® SMI 20/50 μg	CFC-MDI 40/100 μg	Total
Enrolled				691
Entered and treated (safety population)	178	180	177	535
Clinic spirometry ITT[2]	178	180	177	535
Clinic spirometry PP[3]	153	154	154	461
Morning PEFR PP[4]	169	167	169	505
Evening PEFR PP[4]	169	169	170	505
Prematurely discontinued (%)	6 (3.4)	5 (2.8)	11 (6.2)	22 (4.1)

[1]CFC-MDI, chlorofluorocarbon metered-dose inhaler; ITT, intention-to-treat; PEFR, peak expiratory flow rate; PP, per-protocol; SMI, Soft Mist™ Inhaler.
[2]Patients whose forced expiratory volume in 1 sec (FEV_1) was measured before first dose of randomized treatment and at least once afterwards.
[3]Clinic spirometry ITT population, minus patients with protocol deviations that would potentially have obscured response to treatment.
[4]Patients who had at least 4 days of PEFR data (either morning or evening) for both run-in and randomized treatment periods, and with no major protocol violations affecting PEFR assessment or recording.

(safety population). The clinic spirometry ITT population also consisted of 535 patients. Of these, 74 were excluded because of 85 serious protocol deviations, which were primarily unsatisfactory lung function tests ($FEV_1 \geq FVC$; n = 59) and concomitant medication violations (n = 10); the patients who were excluded were distributed evenly between the three treatment groups. The remaining patients (n = 461) constituted the clinic spirometry PP population, which was used for the analysis of all primary and secondary spirometry parameters. The PEFR PP populations (for morning and evening PEFR) each contained 505 patients (see Table 1). Twenty-two patients (4%) failed to complete the study because of AEs (n = 12), or for administrative (n = 9) or other (n = 1) reasons. The overall withdrawal rate was slightly higher in the MDI group (6.2%) than in the Respimat® SMI 10/25 and 20/50 groups (3.4% and 2.8%, respectively).

Baseline demographic data and pulmonary function characteristics at screening were comparable across treatment groups (Table 2). The mean age of patients was 10.4 years, and about two-thirds were boys. The median duration of asthma was 6.3 years, and the three treatment groups were well-matched for pulmonary function measurements at screening. Baseline characteristics of the clinic spirometry PP population were similar to those of the clinic spirometry ITT population.

Efficacy

Primary Endpoint

Analysis of the primary endpoint (change from predose in FEV_1 in the first 60 min after dosing ($AUC_{0-1\ h}$) on day 29) in the clinic spirometry PP population showed that the difference between mean values (adjusted for country and treatment baseline on day 1) for Respimat® SMI 20/50 and MDI 40/100 was 0.022 l (lower 2.5% confidence limit (CL), −0.0199 l; $P = 0.0001$). For Respimat® SMI 10/25 and MDI 40/100, the difference was −0.027 l (lower 2.5% CL, −0.0688 l; $P = 0.0123$). For both Respimat® SMI 20/50 and Respimat® SMI 10/25, the lower CL for the treatment difference with MDI 40/100 was above −0.075 l, indicating that neither Respimat® SMI 20/50 nor Respimat® SMI 10/25 was inferior to MDI 40/100. Figure 3 shows the 95% CIs for treatment differences for change in FEV_1 ($AUC_{0-1\ h}$) on day 29 for all groups. The corresponding analysis of primary endpoint in the clinic spirometry ITT population produced similar results to those in the clinic spirometry PP population.

Time-response curves for change in FEV_1 in the first 60 min on day 29 showed similar profiles for the three active treatment groups (Fig. 4), with a rapid onset of action followed by further increases in bronchodilation to the last observation time of 1 hr. The mean response to Respimat® SMI 20/50 was slightly greater than that to Respimat® SMI 10/25.

Secondary Endpoints

The results for the analysis of the change in FEV_1 ($AUC_{0-1\ h}$) on days 1 and 15 mirrored those on day 29. Both Respimat® SMI 10/25 and Respimat® SMI 20/50 were demonstrated to be noninferior to MDI 40/100.

Analyses of other secondary endpoints, namely FEV_1 ($TAUC_{0-1\ h}$) on day 29, peak FEV_1 achieved in the first

TABLE 2— Demographic and Baseline Characteristics of Safety Population (Mean Values Unless Otherwise Indicated)[1]

Characteristic	Respimat® SMI 10/25 μg	Respimat® SMI 20/50 μg	CFC-MDI 40/100 μg	Total
Sex M/F (N)	109/69	121/59	115/62	345/190
Age, years (range)	10.4 (5–15)	10.4 (6–15)	10.5 (6–15)	10.4 (5–15)
Median duration of asthma, years (range)	6.0 (0.17–15)	6.4 (0.08–15)	6.5 (0.17–15)	6.3 (0.08–15)
FEV_1 (l) (SD)	1.74 (0.55)	1.75 (0.52)	1.77 (0.56)	1.75 (0.54)
% predicted FEV_1 (SD)	78 (9)	78 (9)	78 (9)	78 (9)
FEV_1 increase (%) (SD)[2]	24 (11)	23 (13)	24 (12)	24 (12)
FEV_1/FVC (%)	82 (10)	83 (11)	82 (11)	82 (11)
Pulmonary therapies taken during 6 weeks before run-in (%)				
Inhaled glucocorticoids	72	71	69	71
Short-acting inhaled β-agonists	59	57	60	59
Oral antihistamines	28	23	23	25
Inhaled cromoglycate or inhaled nedocromil	17	16	11	15
Inhaled β-agonist + anticholinergic	12	14	12	13
Long-acting inhaled β-agonists	10	12	10	11
Inhaled β-agonist + cromoglycate	4	5	4	4
Inhaled anticholinergics	3	<1	3	2
Oral xanthines	2	<1	6	3

[1]CFC-MDI, chlorofluorocarbon metered-dose inhaler; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; SD, standard deviation; SMI, Soft Mist™ Inhaler.
[2]After two actuations ipratropium bromide/fenoterol CFC-MDI via Aerochamber®.

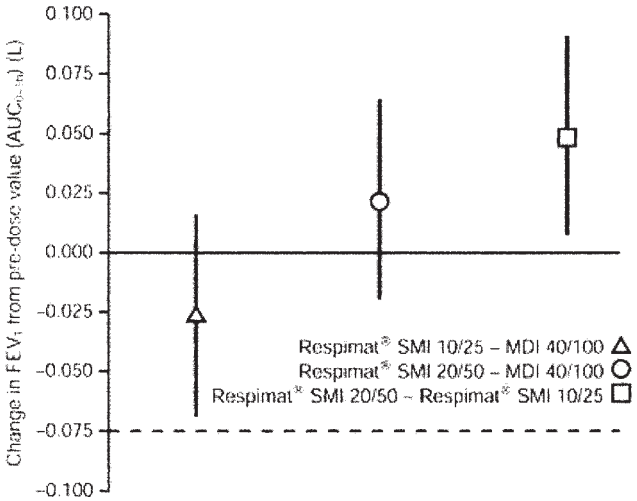

Fig. 3. Between-group differences in bronchodilator response to ipratropium bromide/fenoterol (change in forced expiratory volume in 1 sec. (FEV_1) from predose value expressed as area under curve ($AUC_{0-1\ h}$)) during first 60 min after dosing on day 29 in children with asthma. Differences shown (mean and 95% confidence intervals) are those between each Respimat® Soft Mist™ Inhaler (SMI) group and metered-dose inhaler (MDI) group, and between two Respimat SMI groups, and are adjusted for country and treatment baseline (predose on day 1). Data shown are from clinic spirometry perprotocol population (n = 461).

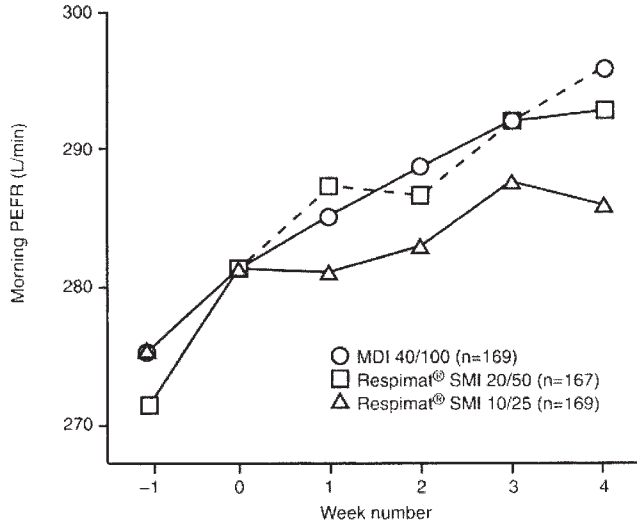

Fig. 5. Mean weekly morning predose peak expiratory flow rates (PEFR) in each treatment group, adjusted for country and treatment baseline (run-in week). Run-in week is last week before first dose of randomized treatment; data shown are from morning PEFR per-protocol population (n = 505). MDI, metered-dose inhaler; SMI, Soft Mist™ Inhaler.

60 min after dosing on days 1 and 29 (measured as change from predose value), and FVC and $FEF_{25-75\%}$ on all test days, gave similar results to those seen for the analysis of the primary endpoint (data not shown). All FEV_1, FVC, and $FEF_{25-75\%}$ analyses showed a trend to higher bronchodilator responses for Respimat® SMI 20/50 than for Respimat® SMI 10/25, with consistently higher point estimates for the higher Respimat® SMI dose (data not shown).

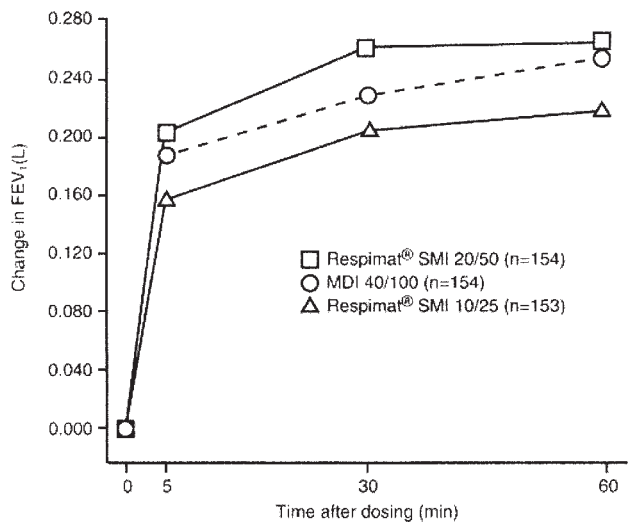

Fig. 4. Mean change in forced expiratory volume in 1 sec (FEV_1) from predose value in first 60 min after dosing with ipratropium bromide/fenoterol on day 29 in three treatment groups, adjusted for country and treatment baseline (predose on day 1). Data shown are from clinic spirometry per-protocol population (n = 461). MDI, metered-dose inhaler; SMI, Soft Mist™ Inhaler.

Diary data showed no clinically relevant differences between treatments. Morning PEFR measurements showed small but steady improvements during the study in all treatment groups (Fig. 5). No treatment difference was observed between Respimat® SMI 20/50 and MDI 40/100; however, the Respimat® SMI 10/25 group had slightly smaller increases in morning PEFR than the other two groups over the study period. The same trends were seen for evening PEFR measurements (data not shown). A small decrease in rescue medication use from the run-in period to the first 2 weeks of randomized treatment was observed in all treatment groups, but no relevant differences were observed between treatments.

Safety and Tolerability

The safety profiles of Respimat® SMI 10/25 and 20/50 were generally comparable to that of MDI 40/100. The overall incidence rate of AEs was higher in the MDI 40/100 (34%) than in the Respimat® SMI 10/25 (25%) and Respimat® SMI 20/50 (24%) groups. However, there were no clinically relevant differences in the incidence of AEs between treatments, and most AEs were mild to moderate in severity. The most commonly reported AEs were respiratory system disorders; the incidence of these and other AEs that were reported by more than 2% of patients in any one group are shown in Table 3. Asthma

TABLE 3— Number of Patients Reporting Adverse Events (AEs) During Randomized Treatment With Ipratropium Bromide/Fenoterol Via Respimat® Soft Mist™ Inhaler (SMI) or CFC-MDI in Children With Asthma (Safety Population, n = 535)[1]

Number of patients (and % of total) reporting at least one adverse event	Respimat® SMI 10/25 μg (n = 178)	Respimat® SMI 20/50 μg (n = 180)	CFC-MDI 40/100 μg (n = 177)
Total with any adverse event	44 (24.7)	43 (23.9)	60 (33.9)
Most common AEs			
Asthma exacerbation	12 (6.7)	10 (5.6)	16 (9.0)
Coughing	11 (6.2)	12 (6.7)	14 (7.9)
URTI	4 (2.2)	8 (4.4)	7 (4.0)
Rhinitis	5 (2.8)	6 (3.3)	5 (2.8)
Pharyngitis	4 (2.2)	4 (2.2)	4 (2.3)
Headache	4 (2.2)	3 (1.7)	5 (2.8)
Sinusitis	3 (1.7)	3 (1.7)	4 (2.3)
Dyspnea	3 (1.7)	0 (0.0)	6 (3.4)
Influenza-like symptoms	1 (0.6)	4 (2.2)	3 (1.7)
Bronchitis	4 (2.2)	1 (0.6)	1 (0.6)

[1]"Most common AEs" are defined as those reported by >2% of patients in at least one treatment group. AEs are described by WHO preferred term. CFC-MDI, chlorofluorocarbon metered-dose inhaler; URTI, upper respiratory tract infection.

exacerbation, coughing, and dyspnea were more frequent in the MDI 40/100 group.

A total of 12 (2.2%) patients discontinued study treatment because of AEs: Respimat® SMI 10/25 (n = 2, 1.1%), Respimat® SMI 20/50 (n = 3, 1.7%), and MDI 40/100 (n = 7, 4.0%). The reasons for discontinuation were unexpected worsening of asthma (n = 6), worsening of other disease (n = 1), and other AEs (n = 5).

Only 4 patients (0.7%) experienced serious AEs during randomized treatment. Three of these were in the MDI 40/100 group (asthma exacerbation, lower abdominal pain of unknown genesis, and appendicitis) and one was in the Respimat® SMI 10/25 group (asthma exacerbation). None of these events was considered to be treatment-related, and all the patients recovered.

Comparison of the first 2 weeks of the randomized treatment period with the last 2 weeks of run-in showed no switch effect in any treatment group, as measured by morning and evening PEFR, rescue medication use, and respiratory AEs. An increase in morning and evening PEFR from run-in to the first 2 weeks of the treatment period was observed in all three groups, accompanied by a fall in rescue medication use. There were no clinically relevant changes in the incidence of respiratory AEs during the first 2 weeks of treatment in the two Respimat® SMI groups compared with run-in (during which they had been receiving open-label IB/FEN MDI). The incidence of asthma exacerbations increased in the MDI group (from 3.4% to 6.2%). Patients in all three groups experienced a slight increase in upper respiratory tract infections (URTIs) in the first 2 weeks of study treatment; however, this finding may have been confounded by the requirement in the study protocol that patients who developed a URTI during run-in were to be excluded from the study.

There were no spontaneous reports of paradoxical bronchoconstriction during the study. There were no clinically relevant differences between treatment groups in vital signs, and no clinically relevant changes were detected by physical examination at the end of the study.

DISCUSSION

The objective of this study was to compare the efficacy and safety of treatment with IB/FEN delivered from a Respimat® SMI with that from a conventional CFC-MDI plus spacer in children with asthma. The results show that not only is IB/FEN via Respimat® SMI at least as effective as via a conventional MDI plus spacer, and just as safe, but that Respimat® SMI also enables a reduction in the nominal dose.

The dosage of IB/FEN used in the active control group (CFC-MDI plus spacer) was two actuations of 20/50 μg taken three times daily. This dosage was chosen because it was the highest dosage shown to be safe in this patient population. However, a quarter and a half of this dosage were considered appropriate for evaluation when delivered from Respimat® SMI (via one actuation, as opposed to two actuations from the CFC-MDI), based on the results from a dose-ranging study[20] and a cumulative dose-response study.[21] The use of a spacer with an MDI is considered the best way of optimizing lung deposition of the inhaled drug. A previous study in healthy volunteers showed that lung deposition from a Respimat® SMI is up to four times greater than that achieved from a MDI used with a spacer.[16]

Analysis of the primary endpoint of this study clearly showed that neither Respimat® SMI 10/25 nor 20/50 was inferior to MDI 40/100 on any of the test days. This result was supported by analyses of secondary endpoints (total FEV_1 ($TAUC_{0-1\ h}$), peak FEV_1 measured as change from predose, FVC, and $FEF_{25-75\%}$). Our results confirm the findings of the dose-ranging and cumulative dose-responses studies in asthma patients already mentioned above;[20,21] these studies showed that administration of IB/FEN via Respimat® SMI was as effective and safe as a dose twice as large (dose-ranging study) or four times as large (dose-response study) given via CFC-MDI. Our results also agree with those of a larger study in patients with asthma: IB/FEN doses of 10/25 μg and 20/50 μg delivered via Respimat® SMI were shown to be non-inferior to IB/FEN 40/100 μg delivered by CFC-MDI in 631 adult patients with moderate to severe stable asthma in a 12-week study.[24]

Goldberg et al. also showed a dose-response relationship (FEV_1 [AUC_{0-6}]) across the range of IB/FEN doses delivered by Respimat® SMI.[20] Similarly, in the current study, all FEV_1, FVC, and $FEF_{25-75\%}$ analyses showed a trend toward a higher bronchodilator response in the Respimat® SMI 20/50 group than in the Respimat® SMI 10/25 group, with higher point estimates for Respimat® SMI 20/50. Since the safety and tolerability of IB/FEN in the two Respimat® SMI groups were very similar, this observation suggests that the Respimat® SMI 20/50 dose is the more rational choice for therapy.

A change of inhaler device and/or formulation may offer the potential for adverse effects to occur, i.e., the so-called ''switch'' effect. However, in our study, comparisons between the first 2 weeks of randomized treatment and the run-in period showed no ''switch'' effect for morning or evening PEFR, rescue medication use, or respiratory adverse events in patients whose treatment changed from CFC-MDI plus spacer to propellant-free Respimat® SMI.

The inclusion of a new inhaler device (Respimat® SMI) required the children in this study to learn a new inhaler technique. Although technique and device preference were not formally measured during the study, anecdotal evidence suggested that children found it easy to learn the correct technique for using the Respimat® SMI, and that they preferred the device to the CFC-MDI. Moreover, the efficacy results achieved with Respimat® SMI (at least as good as with CFC-MDI, but at a lower dose) were achieved without the need for a spacer.

The safety profile of Respimat® SMI 10/25 and 20/50 was comparable to that of CFC-MDI plus spacer. As would be expected in an asthma population, the most common AEs were related to the respiratory system. The incidence of AEs during the 4-week treatment period and the number of children withdrawing from the study were higher in the MDI group than in both Respimat® SMI groups; however, no clinically relevant treatment differences in AE incidence were observed. Therefore, the higher incidence of AEs in the MDI group may be a chance finding.

The use of some inhalers, particularly MDIs, is associated with occasional reports of paradoxical bronchoconstriction, which are assumed to be due to excipients present in the formulation. The aqueous solution delivered by Respimat® SMI contains a stabilizing agent, ethylene diamine tetra-acetic acid, and an antibacterial agent, benzalkonium chloride. These agents, when administered separately, were reported to cause dose-related acute decreases in lung function,[25–27] but at doses that are up to 200 times larger than that contained in a single actuation from a Respimat® SMI. In this study, there were no spontaneous reports of paradoxical bronchoconstriction.

In conclusion, IB/FEN dosages of 10/25 μg and 20/50 μg administered tid from the Respimat® SMI produce bronchodilator responses that are noninferior to a dosage of 40/100 μg administered tid via CFC-MDI plus spacer in children with asthma. Thus, the Respimat® SMI enables a 2–4-fold reduction in the nominal dose of IB/FEN, while offering similar therapeutic efficacy and safety to a CFC-MDI plus spacer over a 4-week treatment period. Respimat® SMI also offers greater convenience, as each individual dose from the Respimat® SMI can be delivered in one actuation as opposed to two from the CFC-MDI. The Respimat® SMI appears to be an improved device for administering inhaled drugs to asthma patients, and obviates the need for a spacer.

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