

Dry Powder Ipratropium Bromide Is As Safe and Effective As Metered-Dose Inhaler Formulation: A Cumulative Dose-Response Study in Chronic Obstructive Pulmonary Disease Patients

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A multi-center, open, randomized, 2-way crossover study was conducted with chronic obstructive pulmonary disease (COPD) patients to compare the safety and efficacy of cumulative doses of ipratropium bromide administered from a pressurized metered-dose inhaler (MDI) or from a breath-activated dry powder inhaler (DPI). Enrolled in the study were 39 patients with moderate to severe COPD and who showed a $\geq 15\%$ increase in baseline forced expiratory volume in the first second (FEV₁) after 80 μg of ipratropium bromide. Thirty-six patients were evaluable for efficacy analysis, and 38 patients were included in the safety analysis group. A significant improvement in pulmonary function was observed following inhalation of cumulative doses of ipratropium bromide (from 20 to 320 μg), but no statistically significant difference was found between the 2 formulations. The dose-response curves were similar. There was no statistical difference in area-under-the-curve during the 180 min period after the last dose for any of the pulmonary function variables. Overall, effects on pulse rate, blood pressure, and QT interval on electrocardiogram were no different between the devices. Six mild adverse events occurred in 4 patients: ventricular ectopic beats on electrocardiogram at 270 min with MDI, bad taste with both MDI and DPI, slight transient increase in blood pressure in the same patient during each study day with both MDI and DPI. Two moderate adverse events occurred in 2 patients: transient ventricular ectopic beats on electrocardiograms with DPI at 270 min, moderate bronchospasm with MDI at 200 min. Patients expressed a preference for DPI, which was found to have a better acceptability and appeared to be easier to use than MDI. The new lactose powder formulation of ipratropium bromide inhaled via the breath-activated DPI is a safe and effective alternative to the chlorofluorocarbon-propelled MDI. *Key-words: chronic obstructive pulmonary disease, COPD, ipratropium bromide, metered-dose inhaler, MDI, dry-powder inhaler, DPI.* [Respir Care 2002;47(2):159–166]

Introduction

Ipratropium bromide is a quaternary ammonium anticholinergic compound chemically related to atropine. Ipratropium bromide induces bronchodilation through a selective parasympathetic blockade of the bronchial muscarinic

receptors.¹ Since cholinergic tone substantially contributes to airway narrowing in patients with chronic obstructive pulmonary disease (COPD), ipratropium bromide is a main-

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stay in the management of those patients.² The bronchodilator action of ipratropium bromide is dose-dependent, and the recommended dose is not a definite dose but rather a range of doses, depending on the subject, the disease, and the severity of the disease. Regular use of ipratropium bromide has been associated with improvement above baseline lung function and in acute response to bronchodilator therapy after 90 days.³ Long-term treatment with ipratropium bromide could be associated with improvement in dyspnea, especially in a subgroup of responder patients who show $\geq 15\%$ increase in baseline forced expiratory volume in the first second (FEV₁) after administration of 80 μg of ipratropium bromide.⁴

Metered-dose inhalers (MDIs) have proven safe, effective, and convenient for delivering ipratropium bromide to COPD patients. However, several drawbacks encountered with MDIs have led to the development and testing of alternative devices such as dry powder inhalers (DPIs). DPIs do not require the coordination of actuation and inhalation that many patients are unable to perform with MDI.⁵ Moreover, DPIs use no propellants, such as chlorofluorocarbon (CFC), which contributes to depletion of the ozone layer in the stratosphere. The Montreal Protocol, which was adopted by several governments in 1987 and has been modified 5 times to date, aims to reduce and eventually eliminate emission of man-made ozone-depleting substances.⁶ In this context, DPI may be a suitable alternative for administering inhaled drugs. Recently a DPI that uses lactose as an excipient was designed for ipratropium bromide inhalation. Earlier powder inhalation formulations of ipratropium bromide used anhydrous glucose as the carrier substance, but the rate and extent of water uptake is less with lactose than with glucose, so the lactose-excipient DPI is less sensitive to environmental humidity than glucose-excipient DPI.

It is therefore important to study the efficacy of the lactose-excipient DPI and to compare its efficacy and safety profile to other established devices. The aim of the present study was to compare the safety and efficacy of ipratropium bromide in COPD patients when taken as an inhaled powder via the lactose-excipient DPI and as a pressurized aerosol via MDI. We used a cumulative dose-response model and also evaluated the tolerability and patient acceptance of the DPI.

Methods

Patients

Thirty-nine patients with clinical diagnoses of COPD (based on American Thoracic Society criteria⁷) were recruited. The study was conducted in accordance with the Helsinki declaration, as amended in Hong Kong in 1989, and the protocol was approved by the Ethics Committee of

University Hospital-Lyon, Lyon, France. Written, informed consent was obtained from each patient before entry into the trial. To be eligible, a patient had to:

- Be over 40 years old
- Have a smoking history of more than 10 pack-years
- Have moderate to severe airway obstruction, with a baseline FEV₁ < 65% of predicted, an initial FEV₁ < 70% of the forced vital capacity (FVC), and a $\geq 15\%$ increase in FEV₁ above baseline 45 min after 80 μg (ie, 4 puffs \times 20 $\mu\text{g}/\text{puff}$) of ipratropium bromide via MDI.

Exclusion criteria were: severe cardiovascular disturbance, history of cancer within the last 5 years, thoracotomy, bronchiectasis, cystic fibrosis, history of asthma, allergic rhinitis, atopy, eosinophil count above 500/mm³, current abuse of alcohol or other drugs, and intolerance to inhaled ipratropium bromide or lactose. No patient should have experienced a respiratory infection nor have been hospitalized for an exacerbation within 6 weeks of the study. Cromolyn sodium, nedocromil, β blocker medication, and long-term oxygen therapy were not allowed throughout the trial, but inhaled corticosteroids could be used, provided that the dose remained unchanged for at least 6 weeks prior to the study and that they were continued at the same dose and taken at the same time of day throughout the trial period. Oral steroid therapy was not an exclusion criterion if daily doses were < 10 mg prednisone equivalents, provided that the patient had been on such a low-dose therapy for at least 1 year. No patient should have changed the dose of other respiratory medications during the previous 6 weeks. Other medications were withheld for appropriate periods on each study day.

Metered-Dose Inhaler and Dry Powder Inhaler

The MDI is a CFC-propelled device that delivers 20 μg ipratropium bromide per puff. The DPI is a breath-activated inhaler into which is inserted a capsule containing a nominal dose of 20 μg ipratropium bromide. After closing the inhaler, the capsule is pierced at both ends by pushing a button, and the patient inhales through the mouthpiece (Fig. 1). The studied DPI provides inhalable particles with a mass median aerodynamic diameter of 4.3 μm . The average aerodynamic particle mass < 5.8 μm is 6 μg ipratropium bromide. Because of a slight deposit into the device, the average delivered dose is 17.8 μg ipratropium bromide.

Study Protocol

We performed an open, randomized, 2-way crossover study. After a screening visit, each patient was trained to obtain a good technique when inhaling either from an MDI or a DPI and when performing pulmonary function tests. Inhalation techniques were regularly checked afterwards.

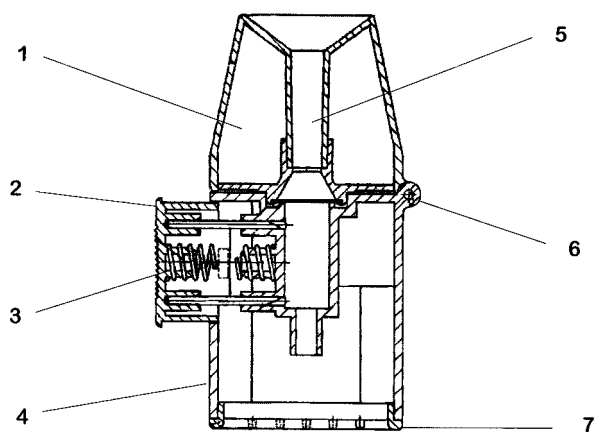


Fig. 1. The dry powder inhaler (DPI). This is a breath-activated inhaler into which a capsule containing 20 μg of ipratropium bromide is inserted. The inhaler is closed, the capsule is pierced at both ends by pushing the button, and the patient inhales through the mouthpiece. 1 = mouthpiece, 2 = piercing button, 3 = spring, 4 = base, 5 = central chamber, 6 = pin, 7 = bottom.

Clinical status was assessed by cardiopulmonary physical examination, and patients were interviewed at the beginning of each study day in order to identify patients with acute exacerbations or recent instability of clinical state.

Baseline pulmonary function tests at inclusion were always determined in the morning, and reversibility was defined as an FEV₁ increase $\geq 15\%$ 45 \pm 5 min after inhalation of 80 μg ipratropium bromide via MDI. The first study day was at least 24 h but not more than 7 d after inclusion. Pre-dose FEV₁ was measured at the same time (\pm 30 min) as baseline FEV₁. Then we recorded FEV₁, FVC, peak expiratory flow, pulse rate, blood pressure, and electrocardiogram (ECG). Five minutes later, the patient took 20 μg ipratropium bromide via MDI or via DPI, according to the randomization. Patients inhaled increasing doses of ipratropium bromide at 50 min intervals, until a cumulative dose of 320 μg was reached. Inhaled and cumulative doubling doses were: 20 μg and 20 μg at 0 min, 20 μg and 40 μg at 50 min, 40 μg and 80 μg at 100 min, 80 μg and 160 μg at 150 min, and 160 μg and 320 μg at 200 min. FEV₁, FVC, heart rate, and blood pressure were measured before and 45 min after each inhalation and at 15–40 min intervals up to 380 min (180 min after the last inhalation). A 45 min interval between each inhalation and pulmonary function measurement was chosen according to the delayed bronchodilator effect of ipratropium bromide and also in order to obtain a substantial accumulation of the compound.

The interval between study Days 1 and 2 was at least 48 h. Protocol requirements during Day 2 were identical to those of Day 1, except for the pre-dose FEV₁, which had to be within a range of 80–120% of the baseline FEV₁ value recorded on Day 1. Otherwise, FEV₁ stability was checked again on 2 consecutive days. If the difference was

still $> 20\%$, the patient was considered nonstable and withdrawn from the study.

Drug wash-out periods before baseline pulmonary functions tests on study Day 1 and study Day 2 were 8 h for short-acting β_2 agonists and anticholinergics, 18 h for oral β_2 agonists, 24 h for short-acting theophylline, 36 h for once-daily oral β_2 agonists, 48 h for long-acting inhaled β_2 agonists and antihistamines, and 72 h for long-acting theophyllines.

The primary outcome measure of the efficacy study was FEV₁ increase between baseline and 45 min after the last dose (195 min). Secondary outcome measures were the FVC increase between baseline and 45 min after the last dose (195 min), the FEV₁ increase at 230–380 min (determined as the area-under-the-curve for FEV₁ increase from baseline divided by the number of hours), and the FEV₁ and FVC values at each time point during each study day. End points for the safety analysis were pulse rate, systolic and diastolic blood pressure, heart rate, and corrected QT intervals measured with a 12-lead ECG performed at baseline and at 270 min.

Patient preferences were evaluated using verbal scales. At the end of Day 1 and Day 2, acceptability of the device was scored from 1 to 4 according to the following scale: 1 = very difficult to use, 2 = quite difficult to use, 3 = rather easy to use, 4 = very easy to use.

Patient preference for either day was assessed as follows: 1 = I prefer the first day of the test, 2 = I prefer the second day of the test, 3 = I have no preference between the 2 days of the test.

Patient preference for one device was assessed at the end of Day 2 by the following question: Do you think the manipulation of the dry powder inhaler is: 1 = less easy than with the metered-dose inhaler, 2 = as easy as the metered-dose inhaler, 3 = somewhat easier than the metered-dose inhaler, 4 = much easier than the metered-dose inhaler.

Statistical Analysis

Statistical analysis was performed with a commercially available software package (Statistical Analysis System, SAS Institute, Cary, North Carolina). All values are expressed as mean \pm SD, except on the graphs, where mean \pm SEM are presented, and statistical significance was taken as $p < 0.05$ (2-sided). A population size of 36 patients was calculated to obtain a 90% power to detect at least a 10% difference in FEV₁ variations between the 2 devices.

Results

Population and Study

The trial population consisted of 39 male patients included by the 7 centers that participated in the study. Six

Table 1. Characteristics of the Patient Population for Efficacy Analysis

	DPI-MDI (n = 19)	MDI-DPI (n = 17)
Age (y)	59.0 ± 7.3	61.8 ± 9.2
Smoking status (pack-years)	43 ± 11	35 ± 11
Concomitant respiratory therapies (n)		
β ₂ agonists	16	14
anticholinergics	10	9
corticosteroids	6	10
theophyllines	6	10
others	9	7
Body height (cm)	167 ± 4	168 ± 7
Body weight (kg)	73 ± 12	73 ± 18
Pulse rate (beats/min)	78 ± 12	75 ± 9
Systolic blood pressure (mm Hg)	132 ± 9	134 ± 15
Diastolic blood pressure (mm Hg)	78 ± 8	78 ± 12
FVC (L)	2.18 ± 0.55	2.22 ± 0.74
FEV ₁ (L)	1.03 ± 0.26	1.13 ± 0.43
FEV ₁ (% of predicted)	35 ± 9	39 ± 14
FEV ₁ 30 min after dose	1.32 ± 0.31	1.43 ± 0.51
% FEV ₁ ipratropium reversibility	29 ± 9	29 ± 13

DPI = dry powder inhaler
 MDI = metered-dose inhaler
 FVC = forced vital capacity
 FEV₁ = forced expiratory volume in the first second
 There was no difference at inclusion between the 2 sequence groups.
 Except for concomitant respiratory therapies, values are mean ± SD.

patients were included by 6 centers and 3 patients by the last one. The mean age was 59.8 ± 8.4 years (range 44–81 y). The mean duration of COPD was 12 ± 8 years (range 0–36 y). All patients were either active smokers (14/39) or ex-smokers (25/39) with smoking histories of > 10 pack-years (mean 39.8 ± 11.5, range 15–70). Two patients did not perform the complete pulmonary function profiles and were not included in the efficacy analysis but were included in the safety analysis. One patient decided not to participate in the study before the first study day and was not assessable for efficacy or safety analysis. Therefore 36 patients were available for the efficacy analysis and 38 patients for the safety analysis. The interval between Day 1 and Day 2 was 3.5 ± 0.6 d.

Efficacy Analysis

There was no difference between the 2 sequence groups at inclusion (Table 1). Both DPI and MDI produced significant improvement in pulmonary function. Figure 2 shows the FEV₁ cumulative dose-response curves. With both formulations, 80–90% of the bronchodilator response was obtained after the first 2 doses of 20 μg ipratropium bromide. Analysis of variance (ANOVA) showed no significant difference in treatment effect between the 2 devices in term of absolute values (p = 0.60), absolute change from baseline (p = 0.58), or relative change from baseline (p = 0.79). Table 2 shows the calculated FEV₁ area-under-the-curve values. ANOVA showed no statistically signif-

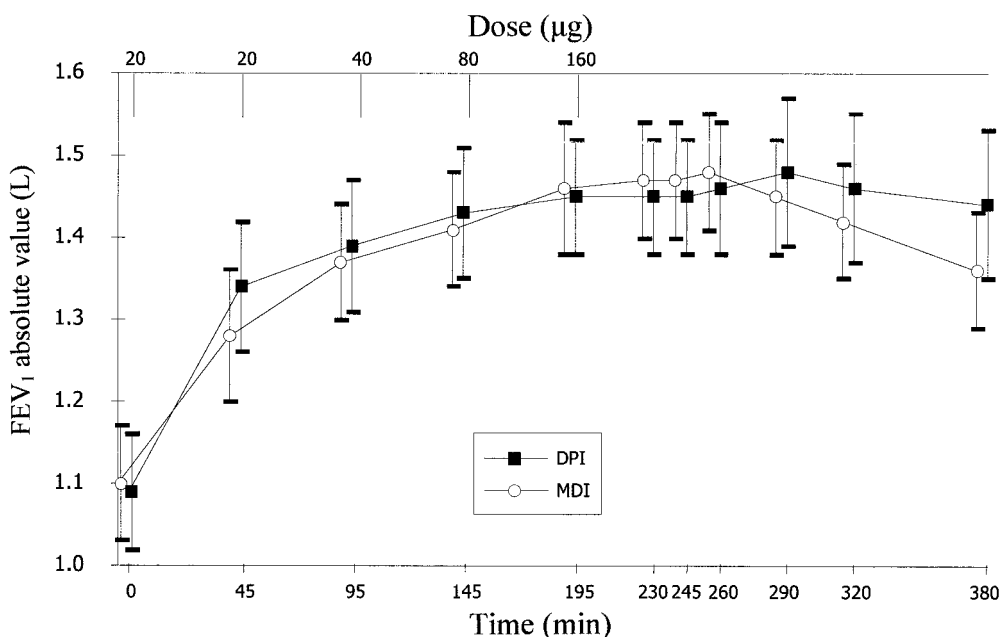


Fig. 2. Dose-response curves of forced expiratory volume in the first second (FEV₁) values. Mean FEV₁ absolute values are shown at baseline (0 min) and after increasing doses of ipratropium bromide delivered via either dry powder inhaler (DPI) or metered-dose inhaler (MDI). Values are mean ± SEM.

icant difference between the treatment groups, either from baseline to 230 min or from 230 to 380 min. Thus, persistence of response was comparable between the devices.

The cumulative dose-response curves of FVC were compared between the 2 treatment groups, and ANOVA showed no significant difference between the 2 devices for absolute values ($p = 0.15$), absolute change from baseline ($p = 0.44$), or relative change from baseline ($p = 0.47$). Figure 3 shows the absolute variations in FVC from baseline. In Table 2, area-under-the-curve values for FVC are given for the 2 parts of the dose-response curve: from baseline to 230 min during the dose-response phase, and from 230 to 380 min during the elimination phase. No significant difference was found between the 2 devices.

Safety Analysis

Six mild adverse events were observed, in 4 patients: ventricular ectopic beats on ECG with MDI at 270 min (70 min after reaching the maximum cumulative dose of 320 μg), bad taste with both MDI and DPI, and slight transient rise in blood pressure (in the same patient during each study day) with both MDI and DPI. Two moderate adverse events were observed, in 2 patients: transient ventricular ectopic beats on ECG with DPI at 270 min (70 min after reaching the maximum cumulative dose of 320 μg) and moderate bronchospasm with MDI at 200 min (just after receiving the maximum cumulative dose of 320 μg). The latter patient received treatment of 5 mg inhaled salbutamol solution and 40 mg intravenous methylprednisolone

Table 2. Area-Under-the-Curve of FEV₁ and FVC Values*

	DPI	MDI
FEV ₁ absolute values -5 to 230 min (L)	323 ± 104	318 ± 102
FEV ₁ absolute values 230 to 380 min (L)	219 ± 73	213 ± 65†
FEV ₁ absolute changes -5 to 230 min (mL)	65 ± 38	60 ± 39
FEV ₁ absolute changes 230 to 380 min (mL)	55 ± 35	51 ± 39†
FVC absolute values -5 to 230 min (L)	615 ± 142	600 ± 153
FVC absolute values 230 to 380 min (L)	410 ± 102	402 ± 107†
FVC absolute changes -5 to 230 min (mL)	110 ± 68	100 ± 71
FVC absolute changes 230 to 380 min (mL)	88 ± 60	86 ± 81†

*n = 36

FEV₁ = forced expiratory volume in the first second

FVC = forced vital capacity

DPI = dry powder inhaler

MDI = metered-dose inhaler

Values are mean ± SD.

†n = 35

Analysis of variance showed no statistically significant difference between the treatment groups, either from baseline to 230 min or from 230 to 380 min.

hemisuccinate, and the bronchospasm stopped after 100 min.

By ANOVA, dose-response curves for absolute values and absolute changes of pulse rate were not statistically different between the 2 groups from baseline to 380 min ($p = 0.63$ and $p = 0.13$, respectively). Furthermore, no significant dose effect was found, even until 380 min ($p = 0.35$), indicating that cumulative doses up to 320 μg of ipratropium bromide have no effect on pulse rate. Twenty-four to 48 hours after the end of the study day, mean pulse

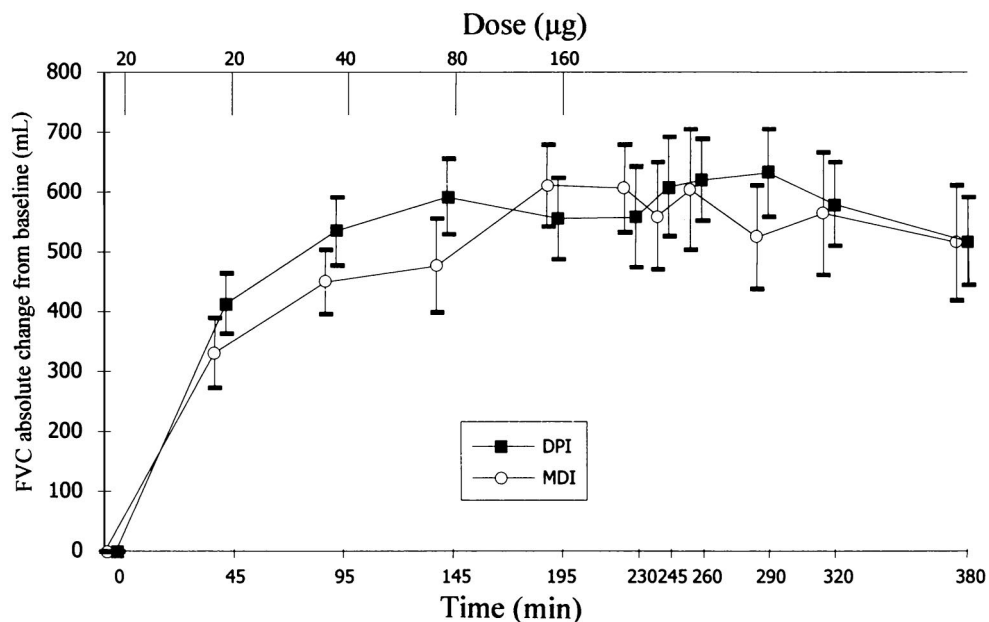


Fig. 3. Dose-response curves of forced vital capacity (FVC) changes from baseline. Mean FVC absolute changes from baseline are shown from baseline (0 min) and after increasing doses of ipratropium bromide delivered via either dry powder inhaler (DPI) or metered-dose inhaler (MDI). Results are expressed as mean ± SEM.

rate was not different between the groups (78 ± 11 beats/min with DPI vs 78 ± 12 beats/min with MDI, $p = 0.90$).

Heart rate and corrected QT interval on ECG measurements were unchanged after the cumulative dose administration, and these were similar in both groups. No interaction, sequence effect, or diurnal effect was found in this analysis.

ANOVA of absolute values and absolute changes in systolic blood pressure found no significant dose or time effect (respectively, $p = 0.94$ and $p = 0.90$ from baseline to 230 min, and, respectively, $p = 0.39$ and $p = 0.29$ until 380 min). ANOVA of absolute values and absolute changes of diastolic blood pressure found no significant dose or time effect (respectively, $p = 0.69$ and $p = 0.61$ from baseline to 230 min, and, respectively, $p = 0.58$ and $p = 0.48$ until 380 min). Twenty-four to 48 hours after the completion of the study days, diastolic and systolic blood pressures were no different between the groups.

Patient Acceptability

The handling of the DPI was considered easier than the MDI ($p = 0.014$), and the DPI was preferred to the MDI ($p < 0.001$). The patient ease-of-use scores (mean \pm SD) were 3.72 ± 0.45 for the DPI and 3.31 ± 0.71 for the MDI ($p = 0.014$). The patient preference scores (mean \pm SD) were 3.17 ± 0.45 for the DPI, and 2.64 ± 0.68 for the MDI ($p < 0.001$). Fifty-six percent of the patients considered the DPI easier to use than the MDI.

Discussion

The bronchodilator action of ipratropium bromide is a dose-dependent phenomenon; the recommended dose is not a *definite* dose but a *range* of doses, depending on the subject, the disease, the time, and the severity of the disease.⁸ It is essential that a new device have equal or better efficacy and an equally favorable safety profile as an established device. Moreover, the results must be generated through the entire range of routinely given doses. To comply with those requirements, a comparison is needed not only of single doses but also of dose-response curves. A cumulative dose-response study is more powerful than a single-dose study to detect small bronchodilator and safety differences.^{9,10} Furthermore, such a study permits a safety evaluation of multiple inhalations and accumulation of excipient. Our study was not placebo-controlled because the efficacy of ipratropium bromide had already been established for COPD patients.¹¹⁻¹³

The 2-way cross-over design of our study was chosen to reduce interpatient variability of pulmonary function measurements. The doses of 20 and 320 μg correspond, respectively, to half of the recommended therapeutic dose (40 μg) and to the highest authorized dose. A 20 μg dose

was used to investigate the initial part of the dose-response curve. A 45 min interval was chosen between each inhalation and pulmonary function measurement in relation to the interval to the peak of bronchodilation of ipratropium bromide and also in order to obtain a substantial accumulation of the compound. A double-blind design was not considered appropriate to evaluate the safety profile of different excipients in 2 different formulations. Safety would not be adequately proven by the administration of standard doses, but rather by gradually increasing doses.¹⁴ Cumulative doses are a convenient means to produce more bronchodilation than a single equivalent dose⁹ and are considered a proper means to estimate efficacy and safety of inhaled bronchodilators¹⁰ in real-life situations such as an "as-required" basis or repeated inhalations during an acute exacerbation. One of the advantages of the cumulative dose-response design is that the response can be followed across a wide dose range. Moreover, a dose-response curve allows good discrimination of 2 different inhaled formulations delivering different inhaled doses.¹⁵

A potential bias in the interpretation of our study could be that we used a fully open-labeled design. However, blinding the patients to treatments would have been extremely difficult, since the MDI and DPI devices could not be made identical. A double-dummy design would have solved that problem, but has a serious drawback: such a design would have led to the administration of excipients of both formulations, which would have made interpreting inhalation-related adverse events almost impossible. Thus, the study was open-labeled. In such a study of different devices, blinding the study personnel is a possible option, but would be difficult to implement in 7 centers, since the pulmonary function tests at baseline and after dosing would have to be conducted separately from the administration of the drug, by another technician, in a different room. Few centers would be able to comply with such a protocol because of inadequate staffing (or even areas) dedicated to the study.

Our study shows a large and identical improvement in pulmonary function values with ipratropium bromide delivered via DPI or MDI. With both devices the most important bronchodilating effect is obtained with the lowest doses—about 20% and 30% increase in FEV₁ with cumulative doses of 20 and 40 μg , respectively. The subsequent additional doses did not markedly improve pulmonary function, since the curves reached a plateau level with the highest cumulative doses (about 40% with FEV₁). These results were confirmed by the comparability of pulmonary function area-under-the-curve values measured from 230 to 380 min (elimination part of the curve) as well as from baseline to 230 min (dose-response curve) for both absolute values and variations from baseline. The comparison of area-under-the-curve values covering the period after the last inhalation also shows a similar post-dose profile

for the 2 formulations. Those results are consistent with previous studies comparing a glucose-excipient powder formulation to the pressurized aerosol of ipratropium bromide in patients with COPD^{16,17} or asthma.^{18,19} In a population of COPD patients with acute reversibility after inhalation of bronchodilators, Gross et al performed a cumulative dose-response study using ipratropium bromide via nebulization.¹¹ They used 5 doses from 50–600 µg of nebulized ipratropium bromide and found that the optimal dose in patients with stable COPD is about 400 µg via nebulizer, which is equivalent to 160 µg via MDI. Thus, Gross et al found a similar optimal ipratropium bromide dose to our study, with both MDI and DPI. Moreover, as in our study, they did not observe any adverse effects at any ipratropium bromide dose.

Our results indicate that large doses of inhaled ipratropium bromide (up to 320 µg) have no clinically relevant effect on pulse rate or blood pressure. This is consistent with the remarkably good tolerability and lack of systemic effects of inhaled ipratropium bromide reported in the literature.²⁰ The rate and type of adverse events were similar for both devices. The number of reported adverse events was low, and no severe adverse effects were described. Only one local adverse effect was reported: a bad taste at the end of each study day. One moderate adverse event with MDI was a bronchospasm that required therapy, but which was due to the interruption of other pulmonary medications before the study day. Thus, we conclude that ipratropium bromide has a comparable safety profile when administered via MDI or DPI. Furthermore, the evaluation of handling and acceptability indicates that the DPI was considered easier to use than MDI and was more acceptable to our study population.

Active patient participation is necessary to obtain an adequate inhalation technique with MDI. Most patients and some medical staff²¹ do not acquire satisfactory MDI technique. In addition, MDI is not adapted to elderly or pediatric patients with poor coordination.⁵ Thus, the development of alternative inhaled pharmaceutical forms is important.^{22–24} Dry powder formulations of bronchodilator drugs should be considered a satisfactory alternative to MDI. DPIs are CFC-free and thus safe for the environment, and they are breath-activated and therefore do not require hand-mouth coordination. The DPI device appears to be easier to use and more practical than a conventional MDI and is at least as well tolerated. Such advantages may greatly improve patient compliance.

Conclusions

This study indicates that cumulative doses (20–320 µg) of a lactose-excipient form of ipratropium bromide have efficacy and safety profiles similar to a marketed MDI form of ipratropium bromide among COPD patients. Hence,

ipratropium bromide in a lactose excipient delivered via DPI is a satisfactory and safe alternative to the conventional CFC-propelled MDI.

ACKNOWLEDGEMENTS

We are indebted to Dr Jean-Paul Ciriez, who contributed to the study and to Dr Eric Guemas for his expert contribution to the statistical analysis. Thanks also to Dr Dan Veale and Richard Medeiros for their advice in editing the manuscript.

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