Improved delivery of ipratropium bromide using Respimat® (a new soft mist inhaler) compared with a conventional metered dose inhaler: cumulative dose response study in patients with COPD

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are amongst the commonest of respiratory disorders, and inhalation has long been regarded as the most effective and selective route to treat these conditions. As the drug is targeted to the required site of action, relatively small doses of drug can achieve a rapid therapeutic response with minimal systemic absorption, reducing the risk of adverse reactions. There are various types of device available for the delivery of inhalation medications, including metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulizers. Of these, MDIs are the most commonly used, and have achieved wide patient acceptability, being portable and easy to use. However, most MDIs use volatile chlorofluorocarbon (CFC) propellants, which have been banned in an international agreement on the protection of the stratospheric ozone layer, the Montreal Protocol. At present, the only permitted use of CFCs is in MDIs, and these will be withdrawn in the next few years as acceptable alternatives for delivering respiratory medicines are introduced.

Ipratropium bromide is an anticholinergic agent widely used for bronchodilation in COPD patients. The present

There is a range of possible approaches in replacing CFC propellants (1). Some alternative devices are already available, including MDIs containing hydrofluoroalkane propellants (2), and DPIs (3,4). However, each carries both advantages and disadvantages based on their lung deposition characteristics, reliability, consistency and ease of use (5). Another approach was to design a mechanical means of delivering a drug solution with favourable particle characteristics resembling those produced by ultrasonic or jet nebulizers, while retaining the convenience and ease of use of MDIs. The product of this development strategy, RMT, is a reusable, propellant-free multidose soft mist inhaler (SMI). The aerosol it produces has a narrow droplet size distribution, a high proportion of the dose in the fine particle fraction (mass median diameter <5.8 μm), and a particle velocity about one-fifth of that of the spray released from conventional MDIs (6,7). Small particle size and low velocity are known to be important for optimal lung deposition (8), and RMT has demonstrated improved targeting of the inhaled dose to the lungs in scintigraphic studies in volunteers (9–15). Furthermore, pilot studies in patients with asthma or COPD have shown that the clinical effect of treatments inhaled from RMT is as good or better than that of the same doses inhaled from conventional MDIs (16–19).
study was conducted to determine the safety and efficacy of cumulative doses of ipratropium bromide inhaled from RMT compared with a conventional MDI, in patients with COPD.

Methods

PATIENTS

We studied 36 outpatients presenting with stable COPD as partly defined by the American Thoracic Society (21) as follows:

(i) age > 40 years;
(ii) smoking history of over 10 pack-years;
(iii) baseline forced expiratory volume in 1 sec (FEV₁) ≤ 65% of the predicted value according to standard criteria (22);
(iv) FEV₁/forced vital capacity (FVC) ratio of ≤ 70%.

All 36 patients were ex-smokers, with a mean ± so past consumption of 49 ± 15 (range 20–80) pack-years. All patients exhibited stable airway obstruction responsive to ipratropium bromide, defined as an improvement in FEV₁ ≥ 15% within 1 h after inhaling 2 × 20 µg ipratropium bromide via MDI. Each patient provided written informed consent, and underwent medical examination to fulfil inclusion and exclusion criteria, including lung function assessment, physical examination, haematology, clinical chemistry and 12-lead ECG. Patients with a history of asthma, allergic rhinitis or atopy were excluded. Patients were also excluded if they were pregnant or lactating, had a recent upper respiratory tract infection (≤ 6 weeks prior to screening visit) or change in pulmonary medications, were intolerant or hypersensitive to study drugs or excipients, or if they were receiving chronic oxygen therapy, oral corticosteroids, β-blockers, antihistamines or cromolyn/nedocromil sodium. Stable use of inhaled corticosteroids was permitted. The study was approved by the Hospital Ethics Committee.

STUDY DESIGN

In a randomized, three-period cross-over design, included patients received cumulative doses of ipratropium bromide (Atrovent®. Boehringer Ingelheim) for 1 + 1 + 2 + 4 + 8 puffs inhaled at 50-min intervals from one of three devices (all from Boehringer Ingelheim):

(i) RMT delivering 10 µg puff⁻¹ (RMT-10);
(ii) RMT delivering 20 µg puff⁻¹ (RMT-20);
(iii) CFC-containing MDI delivering 20 µg per puff (MDI-20).

Thus, the total dose was 320 µg on MDI-20 or RMT-20 test days, and 160 µg on the RMT-10 test day. Treatment was open label between devices (RMT vs. MDI) and double-blind within RMT device. Patients were evaluated for pulmonary function (FEV₁, FVC), vital signs and adverse event until 3 h after the last dose, as described below.

PROTOCOL

Each included patient was assigned to receive the three study treatments (RMT-10, RMT-20, MDI-20) in random order on three study days separated by at least 48 h. Inhaled short-acting β₂-agonists and anticholinergics were withdrawn for 8 h prior to screening and test days, and long-acting β₂-agonists and anticholinergics were withdrawn for 48 and 12 h, respectively. Appropriate washout periods were also applied for excluded oral medications. Lung function measurements were performed at baseline then 45 ± 5 min after each dose, plus 60, 90, 120 and 180 min after the last inhalation. Baseline measurements were performed between 07:00 and 10:00 hours, at the same time on each study day ± 30 min for each patient, and the test day proceeded only if baseline FEV₁ values were within ± 20% of the value obtained for that patient on the first test day patients who showed greater FEV₁ variability on three consecutive days were to be withdrawn and replaced. Patients were asked to avoid strenuous exercise over the 12 h preceding lung function measurements and were not allowed cigarettes, xanthine-containing food or beverages, or exposure to cold, smoke, dust or smells from 12 h before the baseline measurement until the end of the last measurement on each test day.

The primary endpoint was the increase from baseline in the average FEV₁ (measured in litres) between 45 and 245 min after the first inhalation. This was calculated by taking the mean of the FEV₁ increases recorded at 45, 95, 145, 195 and 245 min. Secondary endpoints were: (a) the FEV₁ increase (l) from baseline to 45 min after first inhalation; (b) the FEV₁ increase (l) from baseline between 60 and 180 min after the last intake (i.e. at 260–380 min); and (c) the increases from baseline in FEV₁ (%) and FVC (l) at each time point.

Together with lung function tests, vital signs (pulse rate and blood pressure) were measured at pre-dose and then approximately 45 min after each dose step immediately before spirometry on each test day. On the inclusion day and on the final test day, patients also underwent laboratory tests, including measurement of biochemical parameters (potassium, creatinine, serum glutamic oxaloacetic acid transaminase, serum glutamic pyruvic transaminase, alkaline phosphatases, γ-glutamyl aminotransferase, total bilirubin), a complete blood analysis (haemoglobin, haematocrit, full blood count, platelet count) and theophylline levels. In cases of theophylline levels being higher than 15% fall in FEV₁ below baseline and/or the need for rescue medication, and/or spontaneous reporting by the
patient of any event indicative of bronchospasm within 45 min of inhaling test medication.

**STATISTICAL ANALYSIS**

To demonstrate therapeutic equivalence between RMT and MDI, a null hypothesis was proposed that FEV1 measured 45–245 min after the first inhalation dose would differ by more than 0.12 l between the two treatment administrations. Thirty-six patients were required in this trial for an FEV1 equivalence region of ±0.12 l.

Least square means were obtained for per-protocol data using analysis of variance (ANOVA). Three factors (patients, treatment and period) were included in ANOVA, fitted as a main effect. This model was used to analyse FEV1 (45–245 min). The test-day, pre-dose FEV1 was subtracted prior to analysis, in order to reduce the variance. ANOVA was used to compare the average treatment effect for each RMT treatment vs. MDI and to obtain 95% confidence intervals (CI) for the difference between treatments. The least squares means for each time point were obtained by performing a separate ANOVA at each time point using the model described above. These least square means were plotted against time for each treatment. The primary analysis described for FEV1 (45–245 min) was repeated for FEV1 (260–380 min). To correct for time differences, significance levels were adjusted using retrospective powers calculated for equivalence within a sample size of 36 patients.

Adjusted mean changes in blood pressure and pulse rate from baseline (test-day, pre-dose) were calculated for each treatment (using ANOVA at each time point as described above).

Baseline data are presented as mean ± SD, and result as mean ± SE. A P-value of less than 0.05 was considered statistically significant.

**Results**

**PATIENTS**

Thirty-eight patients were randomized, and 36 received all three test treatments. One patient developed acute severe bronchitis 2 days after the first day (treated with antibiotics) and was excluded from all efficacy analyses. Another patient with a history of arrhythmia (treated with disopyramide 200 mg) was withdrawn before the third test day due to abnormal ECG, and was excluded from the per-protocol efficacy analysis but was included in the intent-to-treat analysis. Baseline characteristics (Table 1) and per-protocol efficacy data are therefore presented for the 36 patients (29 male, seven female) who completed the study.

The mean duration of COPD in these patients was 10 months (mean FEV1 1.80 l, corresponding to 52.6% of the predicted value). The patients exhibited significantly reversible COPD (mean change in FEV1 was 30.7% measured 60 min after inhaling two puffs of 20 µg ipratropium bromide via MDI; Table 1).

**PULMONARY FUNCTION**

All ipratropium treatments produced a marked improvement in FEV1 over baseline values (Fig. 1). The FEV1 vs. time curves for both ipratropium doses administered via RMT were similar, exhibiting a rapid onset of action, followed by a further increase in bronchodilation with successive inhalations until a maximal or plateau FEV1 level was achieved. The bronchodilator effect remained substantial at the last observation time, 3 h after the final inhalation dose, for the three treatments. Analysis of the bronchodilation curve shows that a similar bronchodilation (19%) was obtained 45 min after single puff of either RMT-10 or RMT-20, and the plateau was reached after two puffs of RMT-10 or RMT-20. For MDI-20, the bronchodilation curve was more shallow, a plateau FEV1 response being

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**Table 1. Demographics and baseline characteristics of included patients (n=36)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>29/7</td>
<td></td>
</tr>
<tr>
<td>Duration of COPD (months)</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173</td>
<td>8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72</td>
<td>15</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>52.6</td>
<td>8.9</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>72.1</td>
<td>10.6</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>59.4</td>
<td>7.7</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>1.8</td>
<td>0.4</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>3.0</td>
<td>0.6</td>
</tr>
<tr>
<td>FEV1 reversibility (%)*</td>
<td>30.7</td>
<td>7.7</td>
</tr>
</tbody>
</table>

*Change in FEV1 measured 60 min after inhaling two puffs of 20 µg ipratropium bromide via MDI.
achieved somewhat later, after the final inhalation dose (Fig. 1). Thus, maximal FEV\textsubscript{1} values (adjusted mean change from baseline 0.46, 0.49 and 0.49 l) were first observed at 260, 245 and 245 min for MDI-20, RMT-10 and RMT-20 treatments, respectively. Ipratropium inhalation produced adjusted mean ± se increases in FEV\textsubscript{1} at 45–245 min of 0.44 ± 0.021, 0.43 ± 0.021 and 0.36 ± 0.021 for RMT-10, RMT-20 and MDI-20 treatments, respectively. The increase in FEV\textsubscript{1} at 45–245 min was significantly higher for RMT-10 than MDI-20 treatment, even though the dose was half that delivered by MDI, with a mean treatment difference of 0.080 l (95% CI 0.020–0.140 l, P < 0.01). In addition, there was a significant difference between RMT-20 and MDI-20 treatments, both delivering a cumulative dose of 320 \( \mu \)g; the mean treatment difference for the average change in FEV\textsubscript{1} at 45–245 min was 0.076 l (95% CI 0.016–0.136 l, P = 0.01). The bronchodilator effect of the 320 \( \mu \)g cumulative dose delivered via RMT was similar to that of 160 \( \mu \)g via RMT. Similar results were obtained for the intent-to-treat dataset (n = 37), with an overall significant treatment difference for the increase in FEV\textsubscript{1} at 45–245 min (P = 0.017), and greater bronchodilatation with RMT-10 or RMT-20 than MDI-20 (P = 0.01 and 0.02, respectively).

The improved bronchodilatory efficacy was confirmed when evaluating the secondary endpoints of FEV\textsubscript{1} expressed as the average percentage increase from baseline values, and the average increase in FVC between 45 and 245 min. The adjusted average FVC at 45–245 min in the per-protocol group increased from pre-dose by a mean (± se) of 0.5 ± 0.03, 0.5 ± 0.03 and 0.4 ± 0.031 with RMT-10, RMT-20 and MDI-20 treatments, respectively, demonstrating a clear parallelism with the changes in FEV\textsubscript{1}. In addition, all ipratropium treatments showed persistence of the FEV\textsubscript{1} increase over the 3 h following the last inhalation; the mean ± se change in FEV\textsubscript{1} at 260–380 min was 0.42 ± 0.02, 0.43 ± 0.02 and 0.41 ± 0.021 for RMT-10, RMT-20 and MDI-20 treatments, respectively. Average changes in FEV\textsubscript{1} from pre-dose at 260–380 min with RMT-10 and RMT-20 treatments were significantly equivalent to those for MDI-20. This was again supported by the mean ± se changes in FVC at 260–280 min, which were 0.5 ± 0.04 l for all three treatments.

### ADVERSE EVENTS

All patients were included in the safety analysis: 37 had received RMT-10, 36 RMT-20 and 38 MDI-20. A total of 12 adverse events (none serious) were reported by 10 patients (26%); one, seven, two and two patients suffered adverse events on RMT-10, RMT-20 and MDI-20 days and during the between-treatment washout, respectively. The most frequently reported adverse events were mild to moderate headache (five reports, none considered to be drug-related, some requiring paracetamol or acetysalicylic acid treatment) and pharyngeal irritation (three reports, considered to be treatment-related). Other events (one case each of vomiting, oesophagitis, bronchitis and abnormal ECG: left bundle branch block) were not considered to be related to treatment. The number of patients with clinically significant changes in vital signs was low and balanced across the three treatments (Fig. 2). No prominent changes occurred on physical examination or in laboratory screens; there was no clinical reason why these parameters should change, but their measurement allowed a monitoring of patient well-being. Similarly, no drug-related effects were obtained on ECG: only very slight reductions in heart rate and QT\textsubscript{c} were observed, and these effects were similar within the three treatment groups (Table 2). No subject showed any evidence of paradoxical bronchoconstriction.

### Discussion

The results of our study confirm the safety and efficacy of ipratropium bromide administered via RMT. Between 45 min after initial drug inhalation and 45 min after the final dose, greater bronchodilatory effect was obtained from half the cumulative dose of ipratropium (RMT 10 \( \mu \)g per puff) when compared with the MDI (20 \( \mu \)g per puff) (P < 0.01). Bronchodilatory responses to cumulative doses of ipratropium given via RMT were, on average, higher than those produced via MDI administration. Furthermore, bronchodilation produced by ipratropium delivered via RMT was both rapid and sustained for the duration of the study; the plateau response was reached after only two puffs, delivering a cumulative dose of 20 or 40 \( \mu \)g, and was well maintained at 380 min (Fig. 1).

![Fig. 2. Number of patients with clinically significant changes in blood pressure and heart rate (all evaluable patients, n = 37).](image)

**Table 2.** Mean changes in heart rate and QT\textsubscript{c} from pre-dose to 270 min in evaluable patients (n = 37)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Heart rate (beats/min)</th>
<th>QT\textsubscript{c} (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>RMT-10</td>
<td>-5.76</td>
<td>7.3</td>
</tr>
<tr>
<td>RMT-20</td>
<td>-5.36</td>
<td>9.0</td>
</tr>
<tr>
<td>RMT-20</td>
<td>-6.78</td>
<td>9.3</td>
</tr>
</tbody>
</table>
These results are consistent with those previously reported with RMT therapy for asthma and COPD patients. In a pilot study, Maesen et al. studied cumulative doses of ipratropium given to 10 COPD patients via MDI compared with two prototype SMI devices differing in nozzle configuration and emitted particle characteristics (17). Although bronchodilation did not differ significantly between the three treatments, their results showed a trend for better efficacy, with the prototype SMI exhibiting the greatest proportion of fine particles.

RMT produces a particularly fine aerosol, with a high ‘fine particle fraction’ (6,7), which means that aerosol droplets are capable of surviving filtration and impaction mechanisms to achieve deposition in the lungs. Furthermore, the aerosol is emitted slowly from RMT: the particle velocity of 10 ms⁻¹ is approximately five times slower than that from CFC-MDIs (6,7), which reduces the potential for drug impaction in the oropharynx.

Scintigraphic studies have confirmed that superior in vitro particle characteristics (the result of a sophisticated nozzle design) lead to improved lung deposition in vivo (8–14). These studies showed that lung deposition of radiolabelled drug in healthy volunteers inhaling fenoterol or flunisolide via RMT was typically twice that delivered by MDI or MDI plus spacer, while oropharyngeal deposition was reduced. The authors concluded that a reduction in particle size and velocity leads to an improved deposition pattern in the respiratory tract, which could result in enhanced efficacy.

More recently, a series of studies have demonstrated the safety and superior performance of the SMI device, RMT, delivering the β₂-adrenergic agonist fenoterol, or fenoterol plus ipratropium bromide, in asthmatic patients (18–20). As observed in our patients, a rapid onset of effect and similar degree of bronchodilation was achieved at a half the drug dose when administered via RMT compared with MDI, and there were no safety concerns based on adverse events, vital signs or ECG at doses demonstrating therapeutic equivalence.

The results obtained with MDI administration in our study are consistent with those observed in other cumulative dose studies with ipratropium in comparable populations of COPD patients (23–25). The FEV₁ time profiles and standard deviations agreed closely with those observed using the MDI in our study, validating the use of the MDI group as a positive control group. The patients included in the present study were newly diagnosed with mild to moderate COPD, and were responsive to ipratropium bromide. As a result, large improvements were obtained in lung function following ipratropium inhalation, demonstrated by changes in FEV₁ and supported by those in FVC and allowing wide comparability with other studies, including those evaluating different devices or disease states.

The cumulative-dose model which was applied allowed us to study the effects of a high number of inhalations, resembling the type of administration possible for a patient with COPD suffering from an acute exacerbation. Even at the high doses administered, and the increased lung deposition and greater bronchodilation exhibited by RMT, the ipratropium safety profiles were similar to that of the marketed MDI. This profile is in agreement with the previous studies in asthmatic patients, which demonstrated a similar tolerability for treatments delivered via RMT compared with two-fold higher doses delivered via MDI. Indeed, Vincken et al. revealed a slightly lower incidence of tremor and decreases in serum potassium with fenoterol from RMT delivering 50 µg/puff than from the MDI delivering 100 µg/puff (20).

In conclusion, our data indicate that ipratropium bromide has a comparable safety profile when administered either via RMT or MDI. Our results showed no consistent clinically relevant effects on pulse rate or blood pressure, no prominent changes on physical examination or in laboratory screens, and no drug-related effect on ECG. On acute administration in patients with COPD, ipratropium bromide delivered by RMT can produce more effective bronchodilation than the MDI. Hence, RMT may be a useful alternative to MDIs for the administration of bronchodilator and anti-inflammatory agents in the therapy of asthma and COPD. Furthermore, the improved lung targeting by RMT may permit treatment with a lower daily drug dose than inhalation via MDI.

References

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