Comparative efficacy and potency of ipratropium via Turbuhaler® and pressurized metered-dose inhaler in reversible airflow obstruction


ABSTRACT: Ipratropium bromide (IB), typically delivered by pressurized metered dose inhaler (pMDI), is used to treat patients with reversible airways obstruction. Use of the pMDI, unlike the Turbuhaler® (TH), demands co-ordination of actuation with inspiration for efficient use. Two studies were carried out to compare the relative efficacy and potency of IB delivered by TH or pMDI.

Both studies were of a randomized, double-blind and cross-over design. For the efficacy study, 15 patients received a cumulative dose of 160 µg IB via TH or pMDI as doses of 20, 20, 40 and 80 µg at 45 min intervals on two days. Forced expiratory volume in one second (FEV1) was measured prior to and 40 min after dosing. For the potency study, 33 patients received 10, 20 or 40 µg of IB via TH, 20 µg IB via pMDI, or placebo, on five days. FEV1 was recorded prior to and 15–360 min after dosing.

For the efficacy study, there was no difference in FEV1 response to a cumulative dose of IB via pMDI and TH. More than 80% of the maximum effect was seen at the lowest dose (20 µg of IB). Regarding the potency study, the FEV1 response to 20 µg IB administered via pMDI was similar to that of 10 µg via TH; 20 µg via TH was significantly more effective than 20 µg via pMDI (p<0.05).

In conclusion, the efficacy study showed that maximum FEV1 occurred at low doses of IB, negating any opportunity to identify differences between devices. The potency study indicated that the 10 µg dose via TH was of similar efficacy to the 20 µg dose via pMDI, confirming an efficacy ratio of 1.5–2.0:1 for the TH device. Eur Respir J 1997; 10: 1824–1828.

The controversy surrounding β2-agonist bronchodilators has led to a renewed interest in the anticholinergic bronchodilator ipratropium bromide (IB) which has been available for about 20 yrs and has a good safety profile. IB is used to treat patients with reversible airways obstruction, e.g. patients with chronic obstructive pulmonary disease (COPD) [1], elderly patients with asthma [2], and patients still symptomatic despite treatment with β2-agonists [3]. Typically, delivery is by pressurized metered-dose inhaler (pMDI); however, use of the pMDI, unlike the Turbuhaler® (TH) (Astra Draco AB, Lund, Sweden), demands co-ordination of actuation with inspiration for efficient use [4]. Chlorofluorocarbons (CFCs), which act as the propellant gas in most pMDIs, deplete the ozone layer and their use will have ceased by the end of the century. As an alternative, inspiratory flow-driven dry powder devices have been developed. Their advantages include ease of use as well as lack of local irritation and paradoxical bronchoconstriction secondary to the propellants/surfactants [5, 6]. TH, a multidose dry powder inhaler, contains pure drug (budesonide or terbutaline) or IB and lactose as diluent; an inspiratory flow of as low as 30 L·min-1 is sufficient for efficacy from the device [7]. Previous studies with other drugs have shown the TH to be of greater efficacy than the pMDI at the same nominal dose [8–13]. Two studies were undertaken in patients with reversible airflow obstruction: 1) to determine the efficacy of equivalent nominal doses of IB when given by TH compared with pMDI; and 2) to determine the relative potencies of IB given by TH and pMDI.

Materials and methods

The studies were approved by the local Ethics Committee and were conducted in accordance with the guidelines of the Declaration of Helsinki.

Subjects

Patients were enrolled if they fulfilled the following criteria: 1) age >18 yrs; 2) forced expiratory volume in one second (FEV1) 35–80% predicted normal and >1 L; 3) improvement in FEV1 over baseline of >15%, 40 min after 40 µg IB via pMDI with Nebuhaler (Astra...
Draco, Lund, Sweden); and 4) able to use a pMDI and TH efficiently following appropriate instructions. Patients on regular long-acting oral or inhaled β₂ agonists, theophyllines, antihistamines, oxicromip or intermittent non-steroidal anti-inflammatory drugs including aspirin were excluded. The dose of inhaled steroids and antiallergics had to have been stable for 4 weeks (potency study) or 6 weeks (efficacy study) prior to Visit 1 and had to remain stable for the duration of the studies.

Design

Both studies were of a randomized, double-blind and cross-over design. The primary response variable in both studies was FEV₁.

Efficacy study. Fifteen patients received a cumulative dose of 160 μg IB via TH or pMDI at 45 min intervals on two days. FEV₁ was measured prior to and 40 min after dosing.

Potency study. Thirty three patients received 10, 20 or 40 μg of IB via TH, 20 μg IV pMDI or placebo on five days. FEV₁ was recorded prior to and 15–360 min after dosing.

Methods

Patients attended on three (efficacy study) or six (potency study) separate occasions at the same time of day (±30 min) between 08:30 and 09:30 and were asked to comply with the following restrictions prior to each visit: 1) to withhold, if possible, short-acting inhaled and oral β₂-agonists for 12 h and IB for 24 h; 2) to abstain from tea or food and drinks containing caffeine for 8 h; and 3) not to smoke for 1 h. The study medication consisted of: 1) IB TH delivering 10, 20 and 40 μg IB-dose⁻¹ together with lactose diluent and matching placebo TH (Astra Draco AB, Lund, Sweden); and 2) IB pMDI delivering 20 and 40 μg IB together with propellants and lubricants (Atrovent and Atrovent forte; Boehringer Ingelheim, Ingelheim, Germany) and matching placebo MDI (Astra Draco AB, Lund, Sweden). The combination of pMDI and a commercially available Nebuhaler was only used for reversibility testing prior to enrolment; at all other visits patients were given pMDI alone. In order to ensure accuracy of dosing, the pMDI and TH were primed before use in a room other than the study room. For the pMDI, five doses were fired at 10 s intervals into a plastic bag and the first dose was then administered within 30 min. THs were primed 10 times immediately prior to use. Patients were trained in the inhalation technique using an empty TH and placebo pMDI every visit. Inhalation was performed in the sitting, upright position. When using TH, patients were asked to inhale deeply, fully and forcefully from residual volume, aiming at a peak inspiratory flow (PIF) of ≥50 L·min⁻¹. PIF was assessed by a Vitalograph Compact II Spirometer (Vitalograph Ltd, Buckingham, UK) modified to measure PIF through TH. When using pMDI, patients were instructed to inhale as slowly as possible from residual volume with the device being activated at the beginning of inspiration. Patients held their breath for at least 10 s following inhalation of study medication.

Lung function tests were measured with a Vitalograph Compact II Spirometer and the best of three FEV₁ recordings was used for statistical analysis. In both studies, demographic data, baseline FEV₁ after 20 min of rest and reversibility to 40 μg IB via TH within 30 min were recorded. At Visit 1. Patients were excluded if baseline FEV₁ varied by >15% between visits on which study medication was administered. Randomization was carried out via a computer program (Biostatistics and Data Processing, Astra Draco). The sequence of use of TH and pMDI within each study day was randomized independently of the randomization of study drug administration, but remained constant for Visit 2 and 3 for each individual (efficacy study). For the potency study, a randomization block size of five was used for order of treatment and a block size of four for order of device. Eligible patients were assigned sequentially to the lowest available randomization number at the successful conclusion of Visit 2.

Efficacy study. At Visit 2, patients were randomized to receive IB, either via TH or pMDI, with active treatment from the other type of inhaler administered at Visit 3, 2–7 days later. A total cumulative dose of 160 μg IB was given as individual doses of 20, 20, 40 and 80 μg at 45 min intervals. FEV₁ was measured 5 min prior to the first dose and 40 min after dosing. Adverse events were recorded.

Potency study. At Visit 2, patients were randomized to receive single doses of IB (10, 20 or 40 μg via TH or 20 μg via pMDI), or placebo. FEV₁ was measured and adverse events recorded 5 min prior to the drug administration and at 5, 15, 30, 60, 120, 180, 240, 300 and 360 min after dosing. Following a washout period of 2–7 days, treatment was given from the alternative inhalers at Visits 3–6.

Statistical analysis

Efficacy study. The primary response variable, FEV₁, was log transformed and analysed using the linear additive model. Estimates for differences in FEV₁ response between the two devices were made at the 20 μg and 40 μg dose, the mean response over all four doses, the maximum response at any dose and the area under the curve (AUC) of FEV₁ versus time with adjustments for period effects and baseline FEV₁ measured at each visit.

Potency study. The primary response variables were mean FEV₁ as AUC and maximal FEV₁. These were analysed by analysis of variance (ANOVA) after adjustments for period effects and baseline FEV₁. FEV₁, 6 h postdose, was measured as a secondary response variable. A p-value of less than 0.05 was considered significant.

Results

Efficacy study

Fifteen patients (nine females and six males, mean (range) age 60 (37–76) yrs, mean baseline FEV₁ 1.52 (1.02–2.45) L (57% pred), mean reversibility to 40 μg

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IB at Visit 1 (26%) completed the study. All but one patient, whose diagnosis was "unexplained cough", had asthma with a mean duration of 16 (4–25) yrs. Seven patients were nonsmokers and eight exsmokers. Thirteen patients were on inhaled steroids (mean dose 1200 µg·day⁻¹). Nine patients received TH followed by pMDI and six patients received pMDI followed by TH.

In 11 of the 15 patients, inhalation of IB elicited an overall improvement in lung function irrespective of the inhaler device. Two patients failed to respond to IB via TH and pMDI, even at the 160 µg dose, and a further two patients demonstrated reversibility to IB via TH only, even though all four had shown the required >15% reversibility to 40 µg IB via pMDI and Nebuhaler prior to enrolment.

The mean baseline FEV₁ 5 min prior to inhalation of IB was 1.50 L and rose to 1.92 L after IB inhalation through the TH. For the pMDI the values were 1.46 L and 1.86 L, respectively. The mean cumulative dose responses to IB via TH and pMDI did not differ significantly (fig. 1a). Individual dose responses were steep, as evidenced by results obtained when the data were expressed as a percentage of maximum FEV₁ achieved by the patient on the day of measurement (fig. 1b). Fourteen out of 15 patients had a baseline FEV₁ >60% maximum on both study days. Following inhalation of 20 µg IB, irrespective of inhaler device, the smallest improvement in FEV₁ was 80% maximum, while more than half the patients experienced increases >90% maximum (8 of the 15 patients in TH group and seven of the 15 in the pMDI group). At the 40 µg dose, 10 of the 15 patients given IB via TH and eight of the 15 patients using the pMDI experienced increases >95% maximum. Statistical analysis revealed no significant difference between the devices for mean FEV₁ response at 20 or 40 µg, the mean response across all doses, the maximum response at any dose and AUC following adjustment for period effects and baseline FEV₁ (table 1).

### Table 1. – Mean cumulative dose response to ipratropium bromide (IB) via Turbuhaler (TH) and pressurized metered-dose inhaler (pMDI) and mean ratio of TH:pMDI forced expiratory volume in one second (FEV₁) response

<table>
<thead>
<tr>
<th>FEV₁ response⁺</th>
<th>Mean ratio adjusted for period and baseline FEV₁</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TH</td>
<td>pMDI</td>
<td>%  (95 CI)</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.50 (0.5)</td>
<td>1.46 (0.47)</td>
<td>102.9 (98.8–107.1)</td>
</tr>
<tr>
<td>20 µg IB*</td>
<td>1.79 (0.54)</td>
<td>1.71 (0.54)</td>
<td>100.8 (96.1–105.8)</td>
</tr>
<tr>
<td>40 µg IB*</td>
<td>1.88 (0.59)</td>
<td>1.82 (0.59)</td>
<td>101.4 (98.4–104.5)</td>
</tr>
<tr>
<td>Mean</td>
<td>1.88 (0.66)</td>
<td>1.82 (0.60)</td>
<td>101.0 (97.3–104.8)</td>
</tr>
<tr>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>105.5 (94.7–117.6)</td>
</tr>
<tr>
<td>AUC</td>
<td>-</td>
<td>-</td>
<td>105.5 (94.7–117.6)</td>
</tr>
</tbody>
</table>

Mean: comparison of FEV₁ response between the devices across all four doses. Data for the 80 and 160 µg doses are not shown as the maximum responses were achieved at lower doses. Maximum: comparison of FEV₁ response between the two devices at any dose.⁺: values are means (± SD); *: cumulative dose. 95% CI: 95% confidence interval; AUC: area under the curve of FEV₁ response.

**Potency study.** Thirty three patients (12 female, 21 male, mean age 56 yrs, mean baseline FEV₁ 1.65 (1.11–2.51) L (56% pred), mean reversibility to 40 µg IB at Visit 1 30%) completed the study. All but three patients, whose diagnosis was chronic bronchitis, had asthma with a mean duration of 21.5 (2–61) yrs. Fifteen patients were
Table 2. Mean group data for AUC of the FEV1 response, maximum FEV1 and FEV1 at 6 h in response to placebo or IB via TH or pMDI

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TH 10 µg IB</th>
<th>TH 20 µg IB</th>
<th>TH 40 µg IB</th>
<th>pMDI 20 µg IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC of FEV1 response</td>
<td>1.72 (0.5)</td>
<td>1.94 (0.47)***</td>
<td>2.00 (0.50)***</td>
<td>2.01 (0.50)***</td>
<td>1.96 (0.51)***</td>
</tr>
<tr>
<td>Maximum FEV1 L</td>
<td>1.86 (0.47)</td>
<td>2.10 (0.50)***</td>
<td>2.16 (0.54)***</td>
<td>2.18 (0.54)***</td>
<td>2.13 (0.54)***</td>
</tr>
<tr>
<td>FEV1 6 h postdose L</td>
<td>1.63 (0.47)</td>
<td>1.82 (0.48)***</td>
<td>1.84 (0.52)***</td>
<td>1.86 (0.50)***</td>
<td>1.79 (0.52)***</td>
</tr>
</tbody>
</table>

***: p<0.001 versus placebo; *: p<0.05 versus pMDI. Values in parentheses are SD. For definitions see table 1.

Discussion

Our data showed no difference in FEV1 response to a cumulative dose of IB via pMDI and TH, but the FEV1 single dose response to 20 µg IB administered via pMDI was similar to that of 10 µg via TH and the 20 µg TH was significantly better than the 20 µg pMDI, suggesting an efficacy ratio of around 1.5–2.0:1 for the dry powder device compared with the pressurized aerosol inhaler.

Single dose response studies by Allen and Campbell [14] and Hockley and Johnson [15] revealed maximum FEV1 responses to 120 µg IB (compared with 40 µg) and 200 µg (compared with 80 µg), respectively, when given through the pMDI, but although these differences were statistically significant, they were very small and probably clinically irrelevant. These contrasting results may be explained by the preselection of our patients as we only included those with a good response to IB, in order to obtain potential improvements in FEV1 that would be sufficient to compare the efficacy of the two devices.

In 1986, Maesen et al. [16] compared the efficacy of 40 µg IB given as a dry powder formulation in capsules via the Boehringer inhaler and as an aerosol via the pMDI. There was no significant difference between the two devices, but with comparison with the present study, the chosen dose of 40 µg IB might have been at the top of the dose response curve, masking any potential differences between the devices. Previous studies suggest that TH is of greater efficacy than pMDI. Tønnessen et al. [8] observed a significantly greater increase in FEV1 in patients with acute bronchial obstruction after administration of equivalent doses of terbutaline via TH than with pMDI. An open cumulative dose study showed that the relative dose potency for terbutaline inhaled via TH was 1.5 (p<0.05) compared with pMDI for the primary variable FEV1 [9]. In a deposition study using the charcoal-block method, TH delivered approximately twice as much terbutaline to the lungs as the pMDI, and the observed difference was reflected in the greater bronchodilatation following inhalation through the TH [10]. Tønnessen et al. [11] had previously shown that lung deposition of budesonide via TH was twice that from pMDI. This was supported by a clinical study that compared budesonide via Nebuhaler with half the dose via TH. Children in whom the dose was reduced to 50% used significantly less β2-agonist than those on Nebuhaler treatment, but did not differ in other parameters reflecting asthma control [12]. Silbroos et al. [13] studied 102 asthmatic patients who had been stabilized on the lowest possible dose of beclomethasone dipropionate (BDP) via pMDI and Volumatic (Allen and Hanbury's, London, UK) over a 2 yr period. Twenty five per cent of the group was subsequently switched to equivalent doses of budesonide via TH with a significant mean dose reduction of 300 µg over the following 2 yrs. No corresponding reduction could be obtained in patients continuing on BDP via pMDI, again suggesting greater clinical efficacy of the TH device [13]. Engel et al. [17] described a significant increase in morning peak flow in patients with chronic stable asthma treated with budesonide via TH, compared to pMDI, although there was no difference in FEV1.

The small patient population and the steep dose response curves, with nine of the 15 patients on Turbuhaler and five of the 15 on pressurized metered-dose inhaler reaching the maximum response at doses of 40 µg or less,
may have masked any potential difference between the two devices in the efficacy study. Although our studies have demonstrated maximum forced expiratory volume in one second responses at about 20–40 µg ipratropium bromide, it cannot be assumed that this is the optimum dose for all patients; subgroups of patients with asthma and chronic bronchitis may benefit from additional therapy with higher doses of IB. However, in relation to the objectives of our studies it is apparent that, for a given dose, Turbuhaler is of greater efficiency than pressurized metered-dose inhaler for ipratropium bromide with the efficacy ratio ranging 1.5–2.0.

References