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

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Comparative efficacy and potency of ipratropium via *Turbuhaler® and pressurized metered-dose inhaler in reversible airflow obstruction. F.G.E. Böllert, S.P. Matusiewicz, M.H. Dewar, G.M. Brown, A. McLean, A.P. Greening, G.K. Crompton. ©ERS Journals Ltd 1997.*

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 (FEV_1) 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. FEV_1 was recorded prior to and 15–360 min after dosing.

For the efficacy study, there was no difference in FEV_1 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 FEV_1 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 FEV_1 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.
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The controversy surrounding β_2-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 β_2-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 $L \cdot min^{-1}$ 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 (FEV_1) 35–80% predicted normal and >1 L; 3) improvement in FEV_1 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 β_2 agonists, theophyllines, antihistamines, oxitropium 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 FEV_1.

Efficacy study. Fifteen patients received a cumulative dose of 160 μg IB *via* TH or pMDI at 45 min intervals on two days. FEV_1 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 IB *via* pMDI or placebo on five days. FEV_1 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 β_2-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 at Astra Draco and five 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 FEV_1 recordings was used for statistical analysis. In both studies, demographic data, baseline FEV_1 after 20 min of rest and reversibility to 40 μg IB *via* pMDI with Nebuhaler were recorded at Visit 1. Patients were excluded if baseline FEV_1 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. FEV_1 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. FEV_1 was measured and adverse events recorded 5 min prior to the drug administration and at 5, 15, 30, 60, 90, 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, FEV_1, was log transformed and analysed using the linear additive model. Estimates for differences in FEV_1 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 FEV_1 *versus* time with adjustments for period effects and baseline FEV_1 measured at each visit.

Potency study. The primary response variables were mean FEV_1 as AUC and maximal FEV_1. These were analysed by analysis of variance (ANOVA) after adjustments for period effects and baseline FEV_1. FEV_1, 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 FEV_1 1.52 (1.02–2.45) L (57% pred), mean reversibility to 40 μg

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

	FEV1 response+		Mean ratio adjusted for period and baseline FEV1		
	TH	pMDI	%	(95 CI)	p-value
Baseline	1.50 (0.5)	1.46 (0.47)	-		
20 μg IB*	1.79 (0.54)	1.71 (0.54)	102.9	(98.8–107.1)	0.16
40 μg IB*	1.88 (0.59)	1.82 (0.59)	100.8	(96.1–105.8)	0.71
Mean	1.88 (0.66)	1.82 (0.60)	101.4	(98.4–104.5)	0.33
Maximum	-	-	101.0	(97.3–104.8)	0.58
AUC	-	-	105.5	(94.7–117.6)	0.30

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

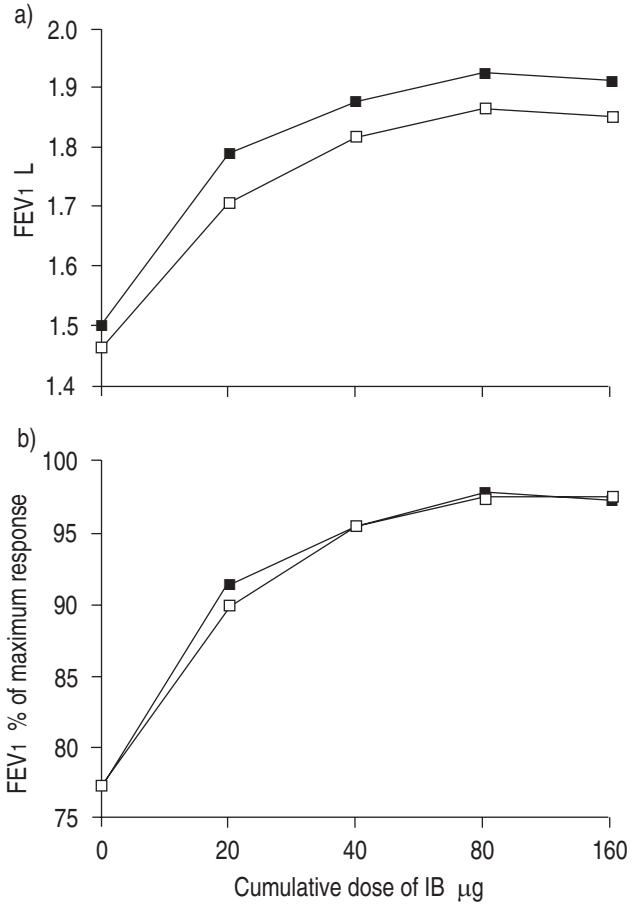

Fig. 1. – Mean forced expiratory volume in one second (FEV1) and cumulative dose response to ipratropium bromide (IB) *via* Turbuhaler (TH) and pressurized metered-dose inhaler (pMDI) in the efficacy study: a) FEV1; b) FEV1 expressed as a percentage of the maximum response. Values are means (n=15). ■ : TH; □ : pMDI.

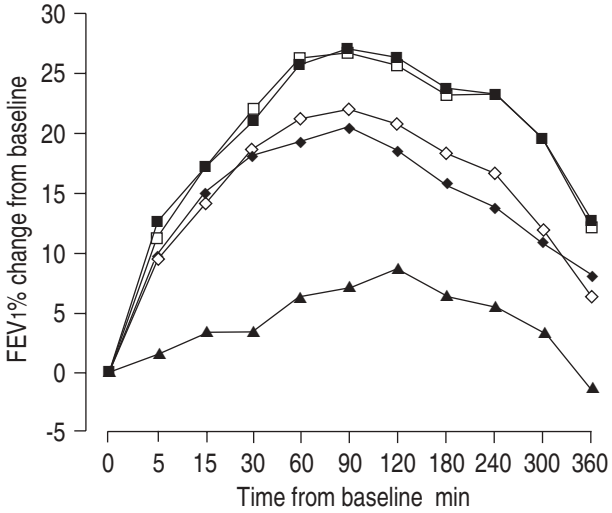

Fig. 2. – Mean FEV1 response expressed as percentage increase over baseline in the potency study. ▲: placebo; ◆: 10 μg TH; □: 20 μg TH; ■: 40 μg TH; ◇: 20 μg pMDI. For definitions see legend to figure 1.

Table 2. – Mean group data for AUC of the FEV_1 response, maximum FEV_1 and FEV_1 at 6 h in response to placebo or IB via TH or pMDI

	Placebo	TH 10 μg IB	TH 20 μg IB	TH 40 μg IB	pMDI 20 μg IB
AUC of FEV_1 response L	1.72 (0.5)	1.94 (0.47)***	2.00 (0.50)***+	2.01 (0.50)***+	1.96 (0.51)***
Maximum FEV_1 L	1.86 (0.47)	2.10 (0.50)***	2.16 (0.54)***	2.18 (0.54)***+	2.13 (0.54)***
FEV_1 6 h postdose L	1.63 (0.47)	1.82 (0.48)***	1.84 (0.52)***	1.86 (0.50)***+	1.79 (0.52)***

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

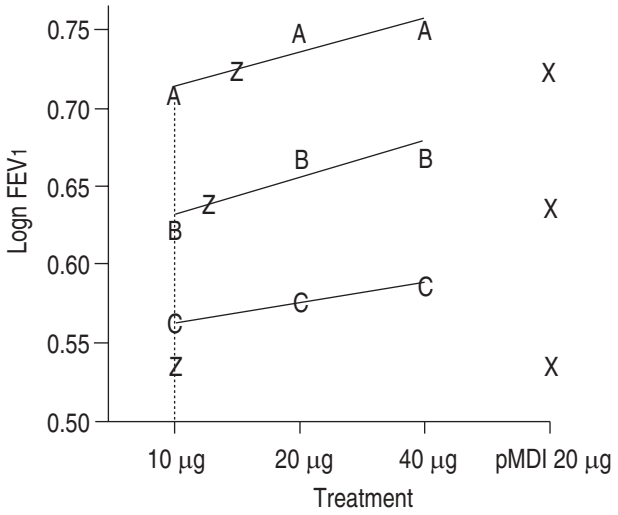

Fig. 3. – Regression on adjusted mean of log transformed FEV_1 to identify relative dose potency of Turbuhaler® compared with pMDI. A: maximum FEV_1; B; mean FEV_1 AUC; C: FEV_1 at 6 h; X: pMDI 20 μg IB; Z: projected pMDI 20 μg IB. For definitions see legend to figure 1.

nonsmokers and 11 exsmokers. Twenty six patients were taking inhaled steroids (mean dose 1000 $\mu g \cdot day^{-1}$), two of these were receiving additional oral maintenance prednisolone (10 $mg \cdot day^{-1}$).

IB elicited a time-dependent rise in FEV_1 that peaked 60–90 min after the dose (fig. 2). All active treatments were better than placebo ($p<0.001$) for the following end-points: AUC of the FEV_1 response; maximum FEV_1; and FEV_1 at 6 h. For AUC of the FEV_1 response, 20 μg IB *via* TH was significantly better ($p<0.05$) than 20 μg IB *via* pMDI, and 40 μg IB *via* TH was more effective than 20 μg IB *via* pMDI for all variables (table 2). However, 20 μg IB *via* pMDI was not significantly better than 10 μg from TH. Figure 3 shows the dose response for the TH compared with pMDI, expressed as the regression of the log transformed and adjusted mean FEV_1.

Discussion

Our data showed no difference in FEV_1 response to a cumulative dose of IB *via* pMDI and TH, but the FEV_1 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 FEV_1 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 FEV_1 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 by 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. TØNNESEN *et al*. [8] observed a significantly greater increase in FEV_1 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 FEV_1 [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]. THORSSON *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 β_2-agonist than those on Nebuhaler treatment, but did not differ in other parameters reflecting asthma control [12]. SELROOS *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 FEV_1.

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.

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