

## Ipratropium Bromide (Atrovent®) as Inhalation Powder

### A Double-Blind Study of Comparison with Ipratropium as a Pressure Aerosol in Patients with Reversible Airways Obstruction

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The bronchospasmolytic effects of 40 µg ipratropium bromide (Atrovent®) given either as an aerosol (2 puffs of 20 µg) or as a powder inhalation were compared in a double-blind cross-over study. Following a randomisation list the drug was given on 2 successive days to 20 patients with stable bronchospasm in whom it had previously been shown that the bronchial obstruction was reversible after administration of 40 µg ipratropium bromide as an aerosol (with an increase over the baseline value of the FEV<sub>1</sub> of at least 15% 1 h after drug administration). The effects of the two presentations of ipratropium bromide were followed by respiratory function tests from 15 min to 6 h after administration of the drug. With both formulations excellent bronchospasmolytic effects were noted in each of the parameters measured. The peak of the effects was noted approximately 1 h after the inhalations. Six hours later there was still a significant improvement in comparison with the baseline values. There was no significant difference between the results with the two different formulations. Inhalation powder of ipratropium bromide was well tolerated and there were no complaints of irritation or coughing. It would appear, therefore, to be a valuable alternative to the pressure aerosol.

*Key words:* asthma; ipratropium bromide; powder inhalation; pressure aerosol.

*Accepted for publication 27 June 1985*

In the management of patients with airways obstruction, treatment with  $\beta_2$  mimetic inhalation powders has in recent times gained an equal place with air pressure aerosols and conventional nebulisers.

The inhalation powder is contained in a capsule as a mixture of active drug with a fine powder composed either of glucose (with a granule size of 2.5 µm) or lactose with a granule size varying from 10 to 80 µm according to the manufacturer (4, 5). Administration as an inhalation powder has certain practical advantages over pressure aerosols, in particular:

It does not demand the accurate synchronisation of inspiration and use of the dispenser which is needed with aerosols employing propellant gas. Such synchronisation appears to cause difficulties (12) in at least 15% of

patients, and children, in particular, find it difficult to co-ordinate.

No propellant gas (chlorofluorocarbon) is inspired. Propellant gas is a hazard to the environment and may cause problems for the patient.

There is less chance of drug overdosage because the inhaler holds no more capsules than are required for the optimal dosage, i.e. 6 capsules per day.

In addition to  $\beta$ -mimetica, ipratropium bromide (Atrovent®), an anticholinergic bronchodilator, has gained a permanent place in the therapy of chronic obstructive respiratory diseases. Both short- and long-term studies have shown that ipratropium bromide is an effective and safe drug (4, 13, 14). Up to now, ipratropium bromide has only been given as an

aerosol, either as a pressure aerosol or with conventional nebulising devices. Recently, however, an inhalation powder of ipratropium bromide has been developed.

We have carried out a study on the effectiveness of ipratropium bromide when given as a powder aerosol in the dose 40 µg, in comparison with the same dose inhaled from a pressure aerosol. The rationale of this investigation is based on former experiences with fenoterol inhalation powder, which, just as ipratropium inhalation powder, also consists of glucose powder. Several studies have demonstrated that fenoterol inhalation powder (200 µg) is equipotent to the same dose inhaled from the fenoterol pressure aerosol (1, 6, 8, 9).

Particular attention has been paid to the occurrence of unwanted drug effects.

MATERIAL AND METHODS

Patient selection

The study, which was a double-blind cross-over trial (double-dummy technique), comprised 20 COLD patients (7 atopics and 13 intrinsic asth-

matics), of whom 6 were female and 14 male. Two patients were excluded from the evaluation, because of differences between the FEV<sub>1</sub> start values on the 2 trial day mornings were more than 15 %. Their ages ranged between 21 and 60 years (mean 46.7, SD 16.7) and all had an initial FEV<sub>1</sub> of at least 1000 ml - ≤ 70 % of the predicted normal value according to the tables of Tammeling (Contours of Breathing, 1978) (Table 1).

The patients were in a relatively stable phase (the difference in initial values on the 2 test days had to be within 15 %) and they showed an FEV<sub>1</sub> reversibility of at least 15 % after two puffs of 20 µg ipratropium bromide (i.e. 40 µg dose) measured 60 min after inhalation. The order of administration on the 2 test days was randomised.

The patients were informed of the nature of the trial by the investigators and all gave their informed consent. The study was approved by the Ethical Committee of the De Wever Hospital.

Treatment

The patients received either 40 µg ipratropium bromide MDI (20 µg/puff) plus one capsule of

Table 1  
Characteristics and baseline lung function data of the patients

| Patient No. | Age (years) | Height (cm) | Weight (kg) | Sex | Reversibility test FEV <sub>1</sub> (l) |                                |
|-------------|-------------|-------------|-------------|-----|-----------------------------------------|--------------------------------|
|             |             |             |             |     | baseline*                               | 60 min after 40 µg ipratropium |
| 1           | 23          | 178         | 74          | f   | 2.04 (54)                               | 2.85                           |
| 2           | 23          | 171         | 77          | m   | 2.56 (62)                               | 3.10                           |
| 3           | 69          | 178         | 63          | m   | 1.10 (35)                               | 1.57                           |
| 4           | 53          | 168         | 67          | m   | 1.04 (33)                               | 1.44                           |
| 5           | 61          | 168         | 83          | m   | 1.19 (40)                               | 1.57                           |
| 6           | 32          | 169         | 73          | f   | 1.89 (58)                               | 2.47                           |
| 7           | 62          | 161         | 58          | f   | 1.15 (52)                               | 1.46                           |
| 8           | 25          | 180         | 64          | m   | 2.55 (56)                               | 3.05                           |
| 9           | 65          | 167         | 65          | m   | 1.00 (36)                               | 1.37                           |
| 10          | 30          | 174         | 69          | f   | 2.30 (65)                               | 2.81                           |
| 11          | 54          | 167         | 54          | m   | 1.21 (39)                               | 1.46                           |
| 12          | 44          | 163         | 59          | f   | 1.80 (66)                               | 2.19                           |
| 13          | 50          | 178         | 83          | m   | 2.14 (58)                               | 2.46                           |
| 14          | 57          | 173         | 73          | m   | 1.31 (40)                               | 1.56                           |
| 15          | 48          | 159         | 61          | f   | 1.00 (40)                               | 1.22                           |
| 16          | 21          | 180         | 71          | m   | 2.64 (58)                               | 3.81                           |
| 17          | 60          | 180         | 80          | m   | 2.22 (63)                               | 2.82                           |
| 18          | 64          | 177         | 91          | m   | 2.24 (69)                               | 2.79                           |

\* Data in parentheses expressed as percent of the predicted value.

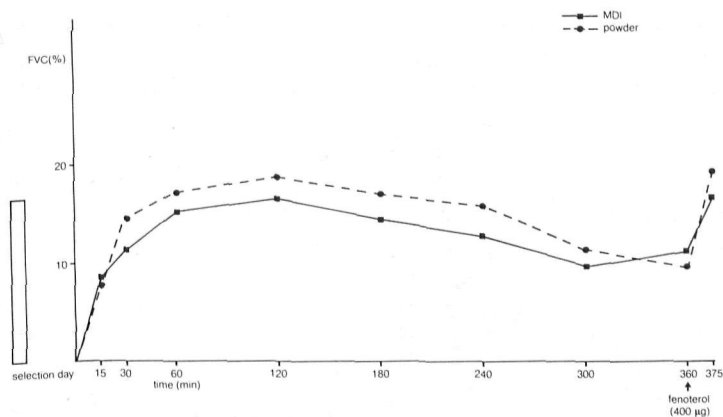


Fig. 1. FVC. Percentage increase from baseline.

Baseline values: 3.50 l MDI  
3.49 l powder

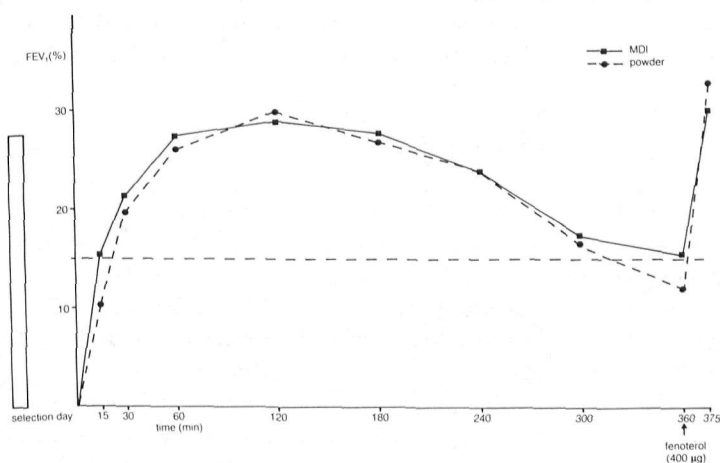


Fig. 2. FEV<sub>1</sub>. Percentage increase from baseline.

Baseline values: 1.78 l/s MDI  
1.75 l/s powder

ipratropium bromide placebo inhaler powder, or two puffs of ipratropium bromide placebo MDI plus one 40 µg capsule of ipratropium inhaler powder on the first day and in reverse order on the second day. At the end of each trial day, i.e. 6 h after inhalation of ipratropium bromide, each patient received two puffs (200 µg/puff) of fenoterol MDI (i.e. 400 µg). All bronchodilator therapy was stopped for at least 12 h prior to the investigation. Corticosteroids were allowed, provided they were taken in a constant low dose throughout the investigation period.

#### Measurements

Lung function tests (FVC, FEV<sub>1</sub>, PEF, FEF<sub>25</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>, FEF<sub>25-75</sub>) were performed at the following time intervals: 5 min before media-

tion and 15, 30, 60, 120, 180, 240, 300 and 360 min after ipratropium bromide administration, and 15 min after additional fenoterol administration at 360 min (i.e. measurement at 375 min).

#### Statistical analysis

To test the difference between metered dose and powder inhalations, and to detect a possible interaction between time and device, a 3-way analysis of variance (ANOVA) was used (mixed model; fixed factors: time, device; random factor: patients). A significance level of 0.05 was chosen. This test was performed both for the absolute values and the values as difference from the baseline. In addition, but only for the FEV<sub>1</sub>, the ANOVA was performed for the difference from baseline as percentage of the baseline.

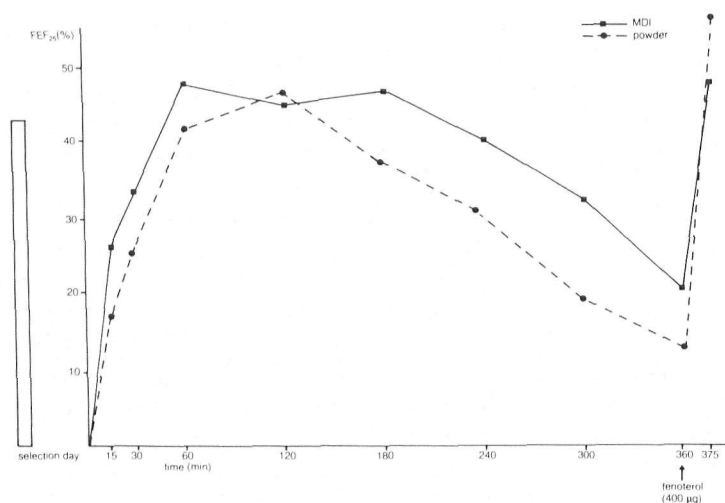


Fig. 3. FEF<sub>25</sub>. Percentage increase from baseline.

Baseline values: 1.95 l/s MDI  
1.94 l/s powder

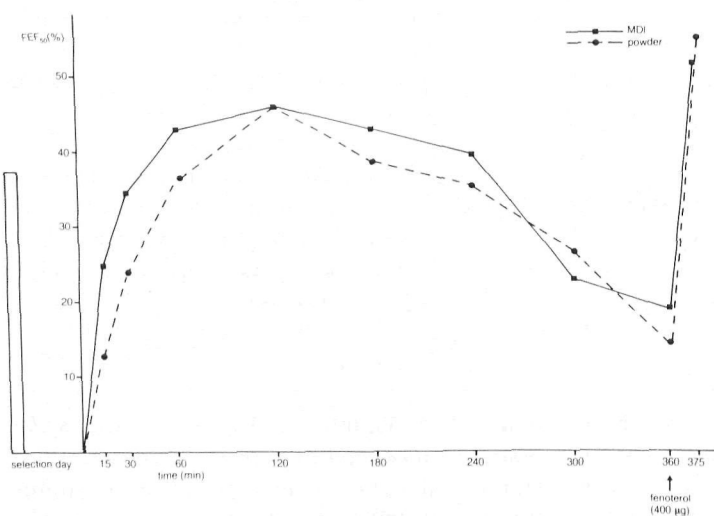


Fig. 4. FEF<sub>50</sub>. Percentage increase from baseline.

Baseline values: 0.98 l/s MDI  
0.95 l/s powder

Further, 95 % confidence intervals of the difference between metered dose inhaler and powder inhaler (mean of the times of measurement) were computed. This analysis was performed because the aim of the study was to ascertain whether metered dose inhalers and powder inhalers differed in efficacy. Confidence intervals were computed for the absolute values and for the values as differences from the baseline. A 95 % confidence interval indicated the range in which, with a security of 95 %, the mean difference between metered dose inhaler and powder inhaler measurements lay. If the 0 (zero) lay within this range there would be no

significant difference between the two devices. If the 0 (zero) lay outside this range, there would be a significant difference between the two devices.

## RESULTS

The results are presented graphically as time-response curves in Figs. 1-7 and expressed as percentage increase in comparison with baseline values. The selection test results can be found on the left of the curve.

The FVC values showed no significant difference between the metered dose inhaler and

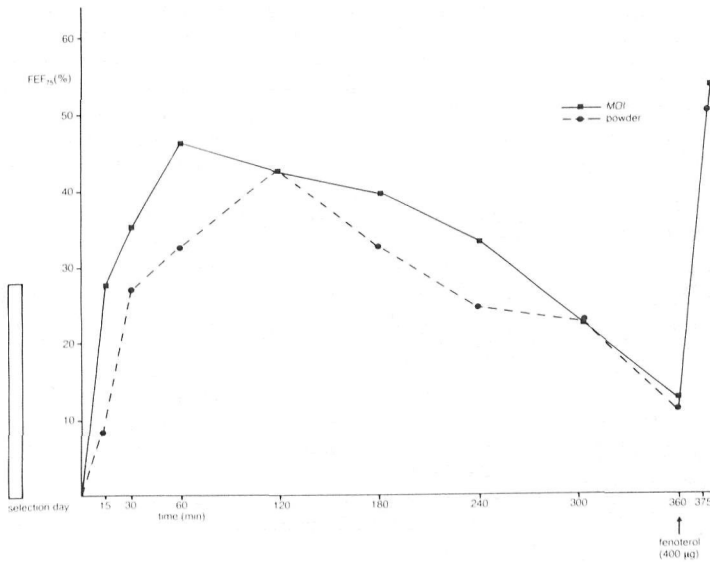


Fig. 5. FEV<sub>75</sub>. Percentage increase from baseline.

Baseline values: 0.37 l/s MDI  
0.34 l/s powder

the powder inhaler (mean absolute values:  $P = 0.48$ ; mean absolute minus baseline values:  $P = 0.32$ ) (Fig. 1).

Fig. 2 shows the FEV<sub>1</sub> results. No significant difference was observed between the two formulations (mean absolute values:  $P = 0.13$ ; mean absolute minus baseline values:  $P = 0.51$ ; difference from baseline as percentage of baseline:  $P = 0.60$ ).

PEF: No significant difference was found between the two inhalation systems (mean absolute values:  $P = 0.085$ ; mean absolute minus baseline values:  $P = 0.16$ ).

FEF<sub>25</sub>: The analysis of variance showed no significant difference between the drug means (mean absolute values:  $P = 0.13$ ; mean absolute minus baseline values:  $P = 0.24$ ) (Fig. 3).

FEF<sub>50</sub>: No significant difference between the two formulations was noted (mean absolute values:  $P = 0.11$ ; mean absolute minus baseline values:  $P = 0.24$ ) (Fig. 4).

FEF<sub>75</sub>: There appeared to be a significant main device effect as shown by the analysis of variance for the mean absolute values ( $P = 0.046$ ), which was caused by the difference from the start values on the 2 trial days. Correction for the difference in baseline value revealed no significant difference between the powder and metered dose inhaler ( $P = 0.26$ ) (Fig. 5).

FEF<sub>25-75</sub>: No significant difference between the two devices (mean absolute values:  $P = 0.063$ ; mean absolute minus baseline values:  $P = 0.15$ ).

There appeared to be no unwanted drug effects. The patients tolerated the powder inhalations without difficulty.

## DISCUSSION

It is well known that most patients with chronic obstructive airways disease react better to  $\beta_2$ -mimetics than to anticholinergic drugs, when given as aerosols (4). This particularly applies to patients with atopic asthma (7). To be certain that the patients were all good responders we only included those patients who had previously shown that they reacted well to 400  $\mu$ g ipratropium bromide from a pressure aerosol by demonstrating an increase of FEV<sub>1</sub> of at least 15% in comparison with the baseline value.

Comparisons between different pharmaceutical preparations of the same active drug are only valid when the patients are known to be good responders. The bronchospasmolytic effect of ipratropium bromide in this selected group was excellent. On average, after less than 1 h, an increase of FEV<sub>1</sub> of at least 25% was achieved and this increase remained constant

for 4 or more hours. At the end of the experiment, 6 h after administration of the active drug, there was still an increase of FEV<sub>1</sub> of approximately 15 % against the baseline values.

The results from both forms of administration appeared to be more or less identical. However, the results of the FVC scored slightly better with the inhalation powder, while those of the PEF and FEF<sub>25-75</sub> were slightly better after the pressure aerosol. The FEV<sub>1</sub> results were the same in both treatment groups.

Two conclusions can be drawn from this study:

1. Ipratropium bromide (Atrovent) given in powder form in a dosage of 40 µg is as good an inhalation therapy as the same dose from a pressure aerosol. It is long-acting and the inhalation material appears to be safe.

2. As the results showed, the bronchospasmolytic effects in this selected group of patients after 400 µg of fenoterol were somewhat better at the end of the study than the peak effects after administration of either of the administrations of 40 µg ipratropium bromide.

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