Comparison of the bioavailability and systemic effects of beclometasone dipropionate suspension for nebulization and beclometasone dipropionate via a metered-dose inhaler after single-dose administration in healthy male volunteers

G. Poli and D. Acerbi

Research and Development, Chiesi Farmaceutici, Parma, Italy

Abstract Pharmacokinetic properties of a drug, and selection and correct usage of an appropriate delivery device, are factors that can affect the outcome of inhaled therapy. The use of nebulization can overcome problems that are associated with other delivery systems used for inhalation therapy. The objective of this open, randomized, single-dose study was to compare the systemic exposure and safety of beclometasone dipropionate (BDP) suspension for nebulization with BDP via metered-dose inhaler (MDI) in healthy subjects. Following a run-in period to assess basal 24-h serum cortisol levels and cortisol urinary excretion, 12 healthy males were administered BDP 1600 μg given via MDI and were then randomized to receive a single dose of either 1600 μg (n=6) or 3200 μg BDP (n=6) suspension for nebulization given via a nebulizer. Results with respect to systemic exposure to beclometasone-17-monopropionate (B17MP) (the active metabolite of BDP) and systemic effects on the hypothalamic–pituitary–adrenal (HPA) axis were determined by evaluation of a number of pharmacokinetic parameters for plasma B17MP and serum and urinary cortisol, respectively. A statistically significantly greater peak plasma concentration (Cmax) of B17MP was reported with BDP via MDI (1587 pg ml⁻¹) compared with BDP 1600 μg (455 pg ml⁻¹) and BDP 3200 μg suspensions for nebulization (758 pg ml⁻¹), and was achieved more rapidly (Tmax) (1.3 h, 3 h, and 2.5 h, respectively). In addition, elimination half-life (t1/2) was statistically significantly shorter with BDP via MDI (4.4 h) than with both dosages of BDP suspensions for nebulization (7.4 h and 6.3 h with 1600 μg and 3200 μg, respectively), as was mean residence time (MRT) (5.4 h, 11.1 h, and 10.0 h, respectively). Total systemic exposure to B17MP (as determined by the area under the concentration–time curve: AUC∞) was comparable for BDP via MDI (6883 pg ml⁻¹ h⁻¹) and BDP 3200 μg suspension for nebulization (8201 pg ml⁻¹ h⁻¹), but significantly greater than with BDP 1600 μg suspension for nebulization (4070 pg ml⁻¹ h⁻¹, F<0.05 vs BDP via MDI). All treatments were well tolerated, and no significant differences were found between them with respect to the serum or urinary cortisol pharmacokinetic parameters assessed. In conclusion, the results of this study demonstrate that BDP suspension for nebulization 3200 μg given via a nebulizer and BDP 1600 μg given via an MDI are equivalent in terms of systemic exposure to B17MP and systemic effects on the HPA axis, with BDP suspension for nebulization having a potentially more prolonged activity. It confirms that use of a double dose of BDP suspension for nebulization administered by nebulizer compared with BDP given via metered-dose inhalation is justified and poses no risk with regard to safety.

© 2003 Elsevier Science Ltd

Keywords: asthma; beclometasone dipropionate; bioavailability; cortisol suppression; metered-dose inhaler; nebulized drugs; suspension for nebulization.

INTRODUCTION

Beclometasone dipropionate (BDP) is a prodrug with weak glucocorticoid receptor-binding affinity and exhibits high topical and low systemic activity. Following inhalation, BDP is primarily hydrolysed in the lung (1) to the topically active metabolite beclometasone-17-monopropionate (B17MP). In turn, B17MP is absorbed and metabolized to beclometasone in the systemic circulation. Plasma levels of unchanged BDP are negligible.

In addition to receptor affinity, prolonged high local concentrations of inhaled steroids in the airways are necessary for effective anti-asthma efficacy and airways selectivity. It has been demonstrated, as observed with budesonide (2), that B17MP within the airways may produce highly lipophilic esters with prolonged...
Retention in the lung tissues (3). These lipophilic esters are stored and then gradually hydrolysed, and free B17MP is subsequently regenerated. The reversible conjugates may prolong the local anti-inflammatory activity of BDP and suggest effectiveness of once-daily administration when used for mild asthma.

As well as the pharmacokinetic properties of a drug, the selection and correct usage of a suitable inhaler device can influence the delivery of inhaled drugs and their subsequent systemic bioavailability, and hence the results of treatment (4,5). Using nebulization for the administration of inhaled steroid therapy can overcome co-ordination and inspiratory problems that may arise with metered-dose and dry-powder inhalers, respectively (6,7).

The purpose of this study was to compare the systemic exposure to B17MP and safety associated with two different doses of a new formulation of BDP suspension for nebulization administered via a nebulizer and BDP administered via a metered-dose inhaler (MDI) in healthy male volunteers.

MATERIALS AND METHODS

Healthy male volunteers, aged 19–43 years, who were non-smokers and in good physical and mental health, and with vital sign values within the normal range, participated in the study.

Study design

This was an open, randomized, single-dose study. Following a run-in period to evaluate basal serum cortisol profile and cortisol urinary excretion, subjects were given BDP 1600 μg via MDI (eight inhalations) (Becotide® 200 μg dose−1, Allen & Hanburys, U.K.) and then assigned by randomization to receive BDP and B17MP levels by means of validated chromatographic methods (LC-MS/MS), with a quantitation limit of 20 pg ml−1, at the Phoenix International Life Sciences Laboratories (Canada).

A total of 10 serum samples were taken over 24 h during the run-in period and after drug administration to measure serum cortisol levels, and urine was collected over 24 h during the same periods to measure cortisol urinary excretion. Cortisol in both serum and urine was determined by means of a validated radioimmunoassay (RIA) method, with a quantitation limit of 10 ng ml−1, at SGS-Biopharma Laboratories (Belgium). B17MP and urinary cortisol pharmacokinetic parameters were calculated using validated SAS® version 6.12 procedures, and serum cortisol pharmacokinetic parameters using WinNonlin Professional 3.0 procedures. The study was approved by the local Medical Ethics Committee of Antwerp (Belgium) and subjects gave their written informed consent. The study was performed in accordance with the principles stated in the Declaration of Helsinki.

Assessments

The main variables assessed were systemic exposure to B17MP by measuring plasma BDP and B17MP levels, and safety by examining adverse events and systemic effects on the HPA axis.

Various pharmacokinetic parameters of plasma B17MP were calculated: Cmax and Tmax (value and time of maximum concentration without interpolation, respectively), AUC0→∞ (area under the concentration−time curve calculated using the trapezoidal method with linear interpolation, from t=0 to t=last measurable data point), AUC0→∞ (area under the concentration−time curve extrapolated to infinity), τ1/2 (elimination half-life), and MRT (mean residence time).

Potential suppression of the hypothalamic–pituitary–adrenal (HPA) axis was assessed by calculating various pharmacokinetic parameters of serum cortisol over a 24-h period, namely Δmax (maximum deviation from run-in), τmax (time of maximum deviation), and AUCΔ (area under the curve of the deviations from run-in), and of cortisol urinary excretion, namely Ae (24-h urinary excretion), Ae norm (%) (24-h urinary excretion normalized for cortisol excretion during run-in), and Ae/Ae creat (24-h urinary excretion normalized for creatinine excretion).

Statistical analysis

For all B17MP and cortisol pharmacokinetic parameters, statistical analysis was carried out using validated SAS® version 6.12 procedures. The main pharmacokinetic parameters for B17MP (Cmax, AUC0→∞, AUC0→∞, τ1/2 and MRT) and cortisol (Δmax, AUCΔ, Ae, Ae norm (%), and...
Ae/Aecreat were statistically compared according to the ANOVA (analysis of variance) using the SAS®/STAT GLM procedure. Tₚ max values were compared according to the non-parametric Wilcoxon scores (Rank Sum) test.

RESULTS

Patient population

Of the 12 subjects who entered the study, one demonstrated atypical serum cortisol and urinary cortisol excretion profiles following BDP administration via MDI, possibly related to a gastrointestinal disorder experienced overnight. The BDP MDI group was therefore made up of 11 subjects for cortisol assessments, and the two BDP nebulization groups of six patients each for all assessments. Subject demography at baseline is reported in Table I.

Evaluation of systemic exposure

Since plasma levels of unchanged BDP were very low and undetectable shortly after inhalation, pharmacokinetic parameter calculations were only carried out for B17MP. Following the administration of BDP via MDI, plasma concentrations of B17MP increased fairly rapidly, resulting in a significantly higher peak and shorter time to peak than observed with either dose of BDP suspension for nebulization (Table 2 and Figure 1). Peak plasma concentrations with BDP 1600 µg and 3200 µg suspensions for nebulization were one-third and one-half lower, respectively, than those seen with BDP administered via MDI. Furthermore, elimination half-life was significantly prolonged with both doses of BDP suspension for nebulization vs BDP via MDI. Total systemic exposure to B17MP, as indicated by AUCₚ max values, was significantly lower (by approximately 30%) with BDP 1600 µg suspension for nebulization than with BDP via MDI, while there was no significant difference between BDP via MDI and BDP 3200 µg suspension for nebulization (Table 2). In addition, MRT values were significantly greater with both doses of BDP suspension for nebulization than with BDP administered via MDI.

Evaluation of safety

Safety data showed that all treatments were well tolerated and had a comparable safety profile. Adverse events reported during the study were mild in severity.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline demographic data for the selected population of healthy male volunteers (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td>Mean value (range)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32 (9–44)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 (60–97)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176 (164–193)</td>
</tr>
</tbody>
</table>

Table 2. Plasma B17MP pharmacokinetic parameters in healthy male volunteers after single-dose administration of BDP suspension for nebulization and via MDI, and BDP administered via MDI

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>BDP 1600 µg suspension for nebulization (n=6)</th>
<th>BDP 3200 µg suspension for nebulization (n=6)</th>
<th>BDP 1600 µg via MDI (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cₚ max (µg/mL)</td>
<td>463 (249–1101)</td>
<td>463 (249–1101)</td>
<td>223 (158–360)</td>
</tr>
<tr>
<td>AUCₚ max (µg·h/mL)</td>
<td>653 (405–1026)</td>
<td>653 (405–1026)</td>
<td>13 (6–9)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>18 (9–32)</td>
<td>18 (9–32)</td>
<td>6.5 (3.5–10.5)</td>
</tr>
</tbody>
</table>

Values are geometric mean (95% confidence interval). AUCₚ max, area under the concentration-time curve from 0 to the last measurable data point; MRT, mean residence time. P<0.05 compared with BDP aerosol spray.
During the run-in period, serum cortisol concentrations dropped from 122 ng ml⁻¹ at 8:00 a.m. to 17 ng ml⁻¹ at midnight before increasing again until 8:00 a.m. the following morning. With all BDP treatments, levels fell more rapidly after administration than during the run-in, such that after 6 h they were below 25 ng ml⁻¹ (compared with just over 75 ng ml⁻¹ during the run-in) (Figure 2). From 6 h to 16 h after administration, serum cortisol levels remained fairly stable at a minimum value and then increased in a similar manner for all treatments to the run-in period until 8:00 a.m. the following day. No significant differences were found between the treatments with respect to any of the pharmacokinetic parameters evaluated for serum cortisol (Table 3).

Cortisol urinary excretion over 24 hours was in the normal range (20–90 µg 24 h⁻¹ according to the RADIM RIA kit) in all subjects except for one, who had values of 18–8 µg 24 h⁻¹ with BDP via MDI and 13–8 µg 24 h⁻¹ with BDP 3200 µg suspension for nebulization. Cortisol urinary excretion normalized for creatinine was virtually unchanged compared with run-in with BDP 1600 µg suspension nebulization, and approximately 10% and 20% lower with BDP 3200 µg suspension for nebulization and BDP via MDI, respectively (Table 4 and Figure 3). Differences between treatments, however, were not statistically significant. Cortisol excretion normalized for run-in showed a similar trend, with reductions vs run-in of approximately 10%, 17%, and 26% with BDP 1600 µg suspension for nebulization, BDP 3200 µg suspension for nebulization, and BDP administered via MDI, respectively.

### Table 3. Serum cortisol pharmacokinetic parameters in healthy, male volunteers after single-dose administration of BDP suspension for nebulization administered via a nebulizer or BDP administered via MDI

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>BDP 1600 µg suspension for nebulization (n=6)</th>
<th>BDP 3200 µg suspension for nebulization (n=6)</th>
<th>BDP 1600 µg via MDI (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔC₀ (ng ml⁻¹)</td>
<td>79 (44–56)</td>
<td>74 (101–55)</td>
<td>79 (113–33)</td>
</tr>
<tr>
<td>Tₘₚ (h)</td>
<td>7 (4–8)</td>
<td>5 (1–24)</td>
<td>4 (1–12)</td>
</tr>
<tr>
<td>AUC/Cₘₚ (ng h ml⁻¹)</td>
<td>-611 (-1114–335)</td>
<td>-542 (-1006–291)</td>
<td>-631 (-965–412)</td>
</tr>
</tbody>
</table>

Values are arithmetic mean. (Exp mean ± SD in data). Values Tₘₚ are median (range).

### Table 4. Urinary cortisol pharmacokinetic parameters in healthy, male volunteers during run-in and after single-dose administration of BDP suspension for nebulization administered via a nebulizer or BDP administered via MDI

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>BDP 1600 µg suspension for nebulization (n=6)</th>
<th>BDP 3200 µg suspension for nebulization (n=6)</th>
<th>BDP 1600 µg via MDI (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in period</td>
<td>Treatment period</td>
<td>Run-in period</td>
<td>Treatment period</td>
</tr>
<tr>
<td>Aenorm (95)</td>
<td>59.9</td>
<td>82.4</td>
<td>74.3</td>
</tr>
<tr>
<td>(54.1–102.6)</td>
<td>(48.7–170.1)</td>
<td>(49.1–110.1)</td>
<td></td>
</tr>
<tr>
<td>Arn/Aenorm (µg g⁻¹)</td>
<td>38.6</td>
<td>37.0</td>
<td>38.0</td>
</tr>
<tr>
<td>(29.4–49.0)</td>
<td>(33.0–42.9)</td>
<td>(31.1–46.6)</td>
<td>(25.0–46.4)</td>
</tr>
</tbody>
</table>

Values are geometric mean. (Exp mean ± SD in data). Values Arn/Aenorm are median (range).

Aenorm=24 h urinary excretion (normalization factor). Arn(Aenorm) excretion during run-in Arn/Aenorm=24 h urinary excretion normalized for creatinine excretion.

Differences between treatments were not statistically significant (P>0.05).
nebulized budesonide on plasma budesonide and plasma cortisol levels, that was independent of the device (9). It was given via nebulizer (8). Conversely, a second study in formulation of BDP suspension given via a nebulizer and 0.8 mg budesonide delivered via MDI and 1 mg and 4 mg adult asthmatics showed a clear dose-related effect of this study was designed to evaluate the systemic influence the amount of drug that is delivered to the lungs, and subsequently the drug's bioavailability (10), and this may explain the inconsistencies to date. The results from this study, using the Pari Turbo Boy® nebulizer, demonstrate significant differences between BDP administered via MDI and BDP suspension for nebulization with respect to several of the pharmacokinetic parameters assessed for plasma B17MP. Administration of BDP via MDI was associated with a more rapid rise to peak plasma concentrations of B17MP (thus suggesting rapid absorption of BDP and subsequent metabolism to B17MP), greater peak plasma concentrations of B17MP, and a notably shorter elimination half-life of plasma B17MP than both the same dose and double the dose of BDP suspension for nebulization. The delayed peak plasma concentration and prolonged elimination half-life of B17MP seen with BDP suspension for nebulization indicate slow and prolonged absorption of BDP from the lung, a hypothesis that is further supported by the MRT values of B17MP, which were significantly greater with both dosages of BDP suspension for when compared with BDP via MDI. Although systemic levels of drugs that exert their topical activity in the lungs are important, more in terms of safety rather than activity, the prolonged elimination half-life and sustained B17MP levels noted with BDP suspension for nebulization may be related to the persistence of BDP at the site of action, thus suggesting potentially prolonged activity compared with BDP administered via MDI. Total systemic exposure to B17MP noted with BDP via MDI, however, was similar to that noted with BDP 3200 µg suspension for nebulization, but considerably greater than with BDP 1600 µg suspension for nebulization. In contrast, no significant differences were found between BDP via MDI and BDP suspension for nebulization with regard to the safety profile, including measures of HPA axis suppression.

In conclusion, this study demonstrates that the systemic exposure to B17MP and systemic effect on HPA axis with BDP 3200 µg given via a nebulizer are comparable with those of BDP 1600 µg given via an MDI. The study also confirms that a double dose of BDP administered via a nebulizer compared with an MDI is justified, and does not present any additional safety risk for the patient.

**REFERENCES**


**FIGURE 3.** Urinary cortisol excretion normalized for creatinine urinary excretion (Ae/Aecreat) in healthy male volunteers during run-in and after single-dose administration of BDP suspension for nebulization administered via a nebulizer or BDP administered via MDI.

(Table 4). Again, differences between treatments were not statistically significant.