Systemic activity of inhaled and swallowed beclomethasone dipropionate and the effect of different inhaler devices

C Trescoli, M J Ward

Summary

Inhaled glucocorticoids such as beclomethasone dipropionate, which are used in the treatment of asthma, may be associated with systemic adverse effects. To determine whether any systemic absorption following the inhalation of beclomethasone was a result of drug being absorbed from the lung (inhaled fraction) or the gastrointestinal tract (swallowed fraction), we studied normal subjects after the inhalation or swallowing of 2 mg beclomethasone dipropionate. Systemic activity was assessed using early morning cortisol suppression. Both inhaled and swallowed fractions produced significant systemic activity, the degree of which depended on the inhaler device used. Systemic activity was greater using a dry powder inhaler (52%) than using a metered dose inhaler with a large volume spacer (28%). These findings suggest that to limit potential adverse effects from high-dose beclomethasone dipropionate it is better to use a metered dose aerosol with large volume spacer than a dry powder.

Keywords: beclomethasone dipropionate; inhaler devices; asthma

Asthma is caused by chronic airway inflammation resulting in periods of airway obstruction. Initially, oral corticosteroids were used to prevent this, but were found to produce serious adverse effects such as vertebral and rib fractures. International guidelines now recommend inhaled anti-inflammatory therapy, and corticosteroids such as beclomethasone dipropionate (BDP) are the most popular agents. Despite the fact that BDP has been used for many years, little is known about its pharmacokinetics and systemic absorption.

Following actuation of an inhaler, some drug is deposited in the lungs and the remainder in the oropharynx, which is swallowed. Inhaled drug may therefore be absorbed from both the lung and gastrointestinal tract, and any systemic activity of the inhaled drug will be the result of combined absorption from both sites. Although there is no clear evidence to implicate inhaled corticosteroids in serious, clinically relevant adverse effects such as osteoporosis, results suggest that inhaled BDP does have an adverse effect on bone metabolism. This led international guidelines to recommend that patients with symptomatic asthma should use inhaled corticosteroids in the lowest dose compatible with control of symptoms.

The present study was set up to determine whether the systemic effects which occur after inhaling BDP are a result of drug being absorbed from the gastrointestinal tract, the lung, or both of these sites. Two different inhaler devices were compared (a metered dose inhaler (MDI) with a large volume spacer, and a dry powder inhaler (DPI) or diskhaler), as different devices deposit different proportions of drug in the gastrointestinal tract and lung. To determine whether the major part of any systemic activity arose from gastrointestinal or lung deposition, BDP was inhaled or taken orally in the absence or presence of activated charcoal in the stomach to bind drug and prevent absorption.

Methods

Twelve healthy non-smoking volunteers inhaled BDP or took it orally. The study was open and all treatments were given in random order to all subjects. Systemic availability of BDP was assessed by measuring change in early morning serum cortisol following a single dose of BDP the preceding night. Volunteers gave written consent to participate in the study and did not take any other medication. The study was approved by the local Ethical Committee.

The treatments given were:

1. Inhaled placebo
2. Inhaled BDP 2 mg by MDI
3. Inhaled BDP 2 mg by DPI
4. Inhaled BDP 2 mg by DPI followed by mouth rinsing and gargling
5. Inhaled BDP 2 mg by DPI with activated charcoal suspension
6. Oral BDP 2 mg powder.
7. Oral BDP 2 mg powder with activated charcoal suspension.

The activated charcoal suspension was made up freshly each time; 10 g were swallowed 5 min before inhaling BDP and 5, 30, 60, and 120 min after. Mouth rinsing and gargling was done twice, each with a minimum of 10 ml water. The water was spat out.

Treatments were taken at 22.00 h. The inhaler technique for each individual was checked beforehand and corrected as necessary by a trained respiratory nurse, so that for a DPI a rapid inhalation from functional residual...
Table 1  Mean early morning cortisol levels (SE) before and after 2 mg BDP. The mean difference in levels between groups, its significance and 95% CI are shown, as well as the percentage difference and the statistical significance of the difference from placebo

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-Rx (SE)</th>
<th>Post-Rx (SE)</th>
<th>Difference</th>
<th>95% CI of difference</th>
<th>p</th>
<th>% change</th>
<th>p of % difference from placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>534 (51)</td>
<td>485 (20)</td>
<td>49</td>
<td>~60 to 158</td>
<td>0.4</td>
<td>~3.5</td>
<td>—</td>
</tr>
<tr>
<td>MDI</td>
<td>481 (53)</td>
<td>317 (39)</td>
<td>164</td>
<td>36.7 to 291</td>
<td>0.016</td>
<td>~28</td>
<td>0.005</td>
</tr>
<tr>
<td>DPI</td>
<td>464 (29)</td>
<td>230 (49)</td>
<td>234</td>
<td>141 to 326</td>
<td>0.0002</td>
<td>~52</td>
<td>0.0005</td>
</tr>
<tr>
<td>DPI + MR</td>
<td>580 (47)</td>
<td>265 (43)</td>
<td>315</td>
<td>209 (47) to 424</td>
<td>0.006</td>
<td>~51</td>
<td>0.0006</td>
</tr>
<tr>
<td>DPI + C</td>
<td>562 (49)</td>
<td>439 (68)</td>
<td>123</td>
<td>~3.3 to 247</td>
<td>0.053</td>
<td>~21</td>
<td>0.04</td>
</tr>
<tr>
<td>Oral</td>
<td>536 (71)</td>
<td>257 (59)</td>
<td>279</td>
<td>136 to 423</td>
<td>0.001</td>
<td>~52</td>
<td>0.007</td>
</tr>
<tr>
<td>Oral + C</td>
<td>506 (46)</td>
<td>458 (57)</td>
<td>48</td>
<td>~148 to 244</td>
<td>0.64</td>
<td>~2.3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

MDI = metered dose inhaler; DPI = dry powder inhaler; MR = mouth rinsing; C = charcoal

capacity was used, while for an MDI a series of three slow breaths was taken from the spacer device. Single puffs were used with the MDI being shaken before each actuation, and inhalation begun as soon after actuation as possible. This was done to optimise lung deposition.

Systemic availability of inhaled and swallowed BDP was assessed by measurement of early morning serum cortisol. Morning serum cortisol was measured at 08.00 h on the morning before a single treatment taken at 22.00 h and at the same time the following day. Volunteers had a minimum 8 h sleep and a minimum wash-out period of 1 week between each part of the study. Cortisol assays were performed using Farmos radio-immunoassay kit with a sensitivity of 5 nmol/l.

Data were analysed using the paired t-test and non-paired t-test (two-sided) where appropriate.

Results

Inhaled and oral BDP produced measurable systemic activity with significant early morning cortisol suppression. The degree of systemic activity was more prominent when the DPI was used. Inhaled BDP as dry powder produced a significant change in mean morning cortisol of ~52% (95% confidence interval (CI) −33.5% to −71%) compared with BDP by aerosol, mean change −28% (95% CI −48% to −8%), and placebo −3.5% (95% CI −15% to 8%), see table. Mouth rinsing did not alter this effect, the mean change in morning cortisol being −53% after 2 mg BDP by dry powder with mouth rinsing (93% CI −67% to −40%).

Swallowed activated charcoal was able to bind BDP in the gut and prevent absorption, this was demonstrated with swallowed BDP. The change in mean cortisol following 2 mg oral BDP was −51% without charcoal and −2.3% (95% CI −24.6 to 26.2%) in the presence of charcoal. This effect was also demonstrated with inhaled BDP, by binding the swallowed fraction following inhalation. The fall in mean cortisol after 2 mg BDP by DPI was reduced from −52% to −21%. This difference of 31% was statistically significant (p=0.04).

When the inhalers are compared, the degree of cortisol suppression was greater with the DPI (52%) than with the MDI (28%).

Discussion

This study assessed hypothalamic–pituitary–adrenal suppression following a single dose of inhaled or oral corticosteroid, the degree of suppression being the product of absorption of active corticosteroid from the lung and the gut, following first-pass metabolism in the liver. It is not possible to infer from this study the long-term effects of inhaled corticosteroids on adrenal function, skin, or bone.

Our results demonstrate that BDP is absorbed to produce systemic activity from both the lung and gastrointestinal tract. Both sites contributed significantly to systemic activity. We were able to demonstrate that oral activated charcoal blocked gastrointestinal absorption of BDP completely. Similarly, swallowed activated charcoal taken prior to inhaled BDP attenuated the fall in serum cortisol. The mean cortisol suppression was −52% before and −21% after charcoal, indicating systemic activity as a consequence of both pulmonary and gastrointestinal absorption.

Mouth rinsing had little effect on systemic absorption, although of course it may still have a beneficial effect in reducing local adverse effects such as oral candidiasis. This may be because of the relatively small surface area of the oropharynx available for systemic absorption compared with the surface area of the alveolar membranes in the lung. Others have demonstrated reduced systemic activity using mouth rinsing, but with a smaller dose of BDP.

By reducing the amount of drug deposited in the oropharynx, an MDI with spacer device increases the dose delivered to the lung whilst reducing the total dose reaching the patient. Consequently, the degree of systemic activity produced by BDP was less with the MDI than with the DPI, a fall of 28% compared with 52%. This finding has clinical implications and would suggest that BDP in high doses should not be given to susceptible patients, such as growing children or menopausal women, as a dry powder. An MDI with spacer device would give the same dose to the lung, but less in total to the patient, and consequently carry less chance of systemic adverse effects. Alternatively, if a DPI is preferred, another corticosteroid with low gastrointestinal absorption and high first-pass metabolism, such as budesonide or fluticasone propionate, could be chosen.
Clostridium difficile-associated diarrhea

N Wight, H Curtis, J Hyde, S P Borriello, Y R Mahida

Summary

At our hospital, the number of cases of *Clostridium difficile*-associated diarrhea increased from 29 in 1993 to 210 in 1995. The case notes of 110 patients with *C. difficile*-associated diarrhea during the first 6 months of 1995 were analysed retrospectively. The majority of the patients (106) had received antibiotics before the onset of diarrhea; 46 had received three or more different antibiotics and 28 had received metronidazole. In 19 patients, the first stool sample after the onset of diarrhea was negative for *C. difficile* cytotoxin, with a mean delay of 8.2 days before a positive stool sample. We conclude that *C. difficile*-associated diarrhea was associated with the usage of multiple antibiotics, and that metronidazole did not protect against colonisation by *C. difficile*. We also recommend that more than one stool sample should be tested for the *C. difficile* cytotoxin.

**Keywords:** *Clostridium difficile*; diarrhea; metronidazole

Table

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of patients taking each antibiotic (%)</th>
<th>Number of patients also taking metronidazole (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephaloridine*</td>
<td>81 (76)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>26 (25)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Ampicillin/amoxicillin</td>
<td>28 (26)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>24 (23)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>17 (16)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Fluconazollic</td>
<td>14 (13)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Ciprofloxacil/loxacin</td>
<td>10 (9)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>6 (6)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2 (2)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1 (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Cetoxafaxime, ceftazoxime, ceftazidime or cephadine

Clostridium difficile is a Gram-positive anaerobic bacillus that is the most commonly encountered bacterial enteropathogen in hospitalised patients. Infection caused by *C. difficile* is an increasing problem as illustrated by a marked increase in the number of reported cases in England and Wales over the last 6 years. At our hospital, the number of cases of *C. difficile*-associated diarrhea (CDAD) has increased from 29 in 1993 to 210 cases in 1995. To investigate this further, we have analysed the case notes of 110 patients with CDAD that occurred in 1995.

**Methods**

Hospital in-patients were identified from records in the microbiology laboratory of all stool samples received between 1 January and 30 June 1995 that were positive for *C. difficile* cytotoxin (detected by standard Vero cell assay). The case notes of the identified patients were retrieved for detailed review. Information was recorded on patient demographics, antibiotic usage, investigations and treatment of CDAD, and outcome. Information on antibiotic usage prior to hospital admission was obtained from the patients' general practitioners.

**Results**

Out of 126 adult patients with CDAD, case notes were available for 110 (87.5%). Most of the patients were elderly, with a median age of 83 years (range 19–98; 53 male, 57 female) and the majority (73.7%) had been nursed on Health Care of the Elderly wards.

Of the 110 patients, 106 (96%) had received antibiotics prior to the onset of CDAD (table). Amongst these patients the use of multiple antibiotics was common, with 81 (76%) receiving two or more and 46 (43%) receiving three or more antibiotics prior to the onset of CDAD. Twenty-eight (26%) patients on antibiotics had received metronidazole, including
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