The comparative safety/efficacy ratio of HFA-BDP

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Introduction

The safety/efficacy ratio, or therapeutic ratio, of an anti-
asthmatic agent is determined by the relationship between
its dose–response relationship for anti-asthmatic clinical
efficacy and its systemic adverse effects (1). An under-
standing of the relative risks and benefits of any anti-
asthmatic agent are vital in order to fully appreciate how
the agent should be used optimally in everyday clinical
practice.

Anti-asthmatic efficacy can be measured through the use
of recognized laboratory or domiciliary clinical endpoints
(such as FEV1, FEF25-75%, AM PEF). However, safety has
to be measured through perhaps a more subtle interaction
of pharmacological and pharmacokinetic parameters,
combined with clinically relevant endpoints such as adverse
events, as well as biochemical, haematological and labora-
tory markers.

Whilst an understanding of the safety/efficacy ratio of
any agent per se is important, it is perhaps of more value to
understand its therapeutic index relative to other available
anti-asthmatic agents, in order that the physician might
choose the optimal therapy for each individual patient. The
aim of this paper is therefore to discuss the relative
comparative safety/efficacy ratio of QVAR™ (3M Phar-
maceuticals, St Paul, MN, U.S.A.) [hydrofluoroalkane-
134a beclomethasone dipropionate (HFA-BDP)] in com-
parison with other anti-asthmatic preparations, by looking
at the influence of pharmacokinetic and pharmacological
factors, device factors, efficacy factors and safety con-
siderations on this parameter.

Relative efficacy of HFA-BDP

The HFA-BDP dose ratio for equipotent efficacy can be
summarized in the following table (Table I). These data
show that switching from a chlorofluorocarbon (CFC)-
BDP formulation to HFA-BDP increases the delivery of
beclomethasone resulting in a 2:1 comparative dose ratio.
In contrast, HFA-BDP has a 1:1 comparative dose ratio
compared to fluticasone pMDI-CFC, a result of (a)
fluticasone showing twice the level of receptor potency
and affinity compared to beclomethasone dipropionate (and
its active metabolite beclometasone-17-monopropionate
(17-BMP)) and (b) HFA-BDP demonstrating twice the
delivery compared to fluticasone pMDI-CFC.

Finally, budesonide and BDP have approximately the
same receptor potency, but as the HFA inhaler delivers
approximately twice that of the budesonide turbohaler,
there is a resultant potency of 2:1.

Relative safety of HFA-BDP

DEVICE FACTORS

The reformulation of beclomethasone from a CFC-based
formulation into an HFA-formulation in QVAR™,

together with improvements in inhaler device technology,
have resulted in an extrafine mean particle size, which has
allowed improved delivery of BDP into the large and small
airways. This has resulted not only in the improved efficacy
discussed previously in this supplement, but also in
improvements in the physical characteristics of the aerosol
plume, producing a warmer and gentler spray compared to
fluticasone pMDI-CFC (2). Thus, the cold freon effect may
be reduced through a combination of reformulation and
device technology. This could conceivably translate into
improved patient compliance and better lung delivery,
because of the lower tendency for gagging due to the cold
freon impact on the posterior oropharynx.

PHARMACOLOGICAL AND
PHARMACOKINETIC FACTORS

Plasma elimination

Lipophilic substitutions of the basic glucocorticosteroid
nucleus affects the volume of distribution and hence the
degree of retention within the systemic tissues (3). For
example, fluticasone and mometasone furoate are very lipid
soluble; in contrast triamcinolone acetonide, budesonide
and 17-BMP have a much lower level of lipid solubility
(Fig. 1).

Drugs with high lipid solubility are found at a relatively
low level in the blood (as blood is mainly water) and at a
relatively high level in systemic tissue (as tissue is mainly
fat). In contrast, compounds which are much less lipid
soluble have a relatively higher concentration in the blood as
compared to the systemic tissue. This will be reflected in the
total volume of distribution (i.e. blood and systemic tissue)
which will be much higher for fluticasone than 17-BMP.
TABLE 1. HFA-BDP dose ratio for equipotent efficacy

<table>
<thead>
<tr>
<th>Inhaled steroid formulation</th>
<th>HFA-BDP µg equipotent efficacy dose ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC-BDP (QVAR)</td>
<td>2:1</td>
</tr>
<tr>
<td>Fluticasone-CFC pMDI (Flixotide)</td>
<td>1:1</td>
</tr>
<tr>
<td>Budesonide-DPI (Pulmicort)</td>
<td>2:1</td>
</tr>
</tbody>
</table>

This difference is important when calculating systemic absorption or total bioavailability. For example, if a blood sample is used to measure the systemic exposure of fluticasone, a falsely low value will result because the bioavailability will have been measured in the wrong compartment. This is because fluticasone propionate has the highest level of lipophilicity amongst the currently available inhaled corticosteroids, which may account for it having a relatively long elimination half-life (14.4 h) (3) (Table 2). This is because there is constant equilibrium between the blood and tissue compartments at steady-state, with the tissue acting, in effect, as a biological slow release reservoir. An analogy is to think of a wet sponge with the drip representing the intravascular drug, and the total systemic exposure representing what comes out when squeezing the sponge.

Although drugs such as 17-BMP triamcinolone acetonide and budesonide have relatively high plasma levels (due to a small volume of distribution), they tend to have much shorter half-lives (between 2–6 h) as they do not equilibrate with systemic tissue to the same degree.

Drug accumulation in blood and tissue occurs when fluticasone propionate is administered twice daily, because its elimination half-life (14-4 h) is longer than the 12-h dosing interval (9).

Pharmacokinetics

Whilst plasma elimination half-lives can give valuable information regarding drug accumulation, such data need to be confirmed through single and multiple dose pharmacokinetic studies, especially as the improved delivery of HFA-BDP to the lungs (with less swallowed) could affect the absorption of BDP. As can be seen from Fig. 2 (10), as the level of a single dose of HFA-BDP increases from 100 to 400 µg there is a linear increase in serum concentration of beclomethasone alcohol. In particular the maximum concentration (C_{max})—a good surrogate for the lung dose due to the very rapid absorption of the drug from the lung into the blood—doubles with doubling of the dose.

With repeated dosing, at steady-state, the serum profile of total beclomethasone from HFA-BDP is very similar to that from single-doses, with the C_{max} again being proportional to the dose. In addition, such multiple dosing to steady-state indicates that very little accumulation of beclomethasone occurs (the accumulation ratio between single and repeated dosing is 1:3), especially when this is compared to fluticasone studies, which suggest an accumulation ratio of approximately three-fold (3).

![FIG. 1. Schematic diagram to illustrate intravascular vs. extravascular distribution with steady-state inhaled corticosteroid. FP: fluticasone propionate; 17-BMP: beclomethasone-17-monopropionate.](image-url)
TABLE 2. Plasma elimination half-life for inhaled steroids

<table>
<thead>
<tr>
<th>Inhaled steroid formulation</th>
<th>T_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>14.4</td>
</tr>
<tr>
<td>Beclomethasone 17-monopropionate</td>
<td>6.5</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>2.5</td>
</tr>
<tr>
<td>Budesonide</td>
<td>2.3</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Source: Refs 3,5-8.

SYSTEMIC SIDE-EFFECTS

Adrenal suppression

The administration of exogenous inhaled corticosteroids results in a negative feedback on glucocorticoid receptors in the hypothalamus and anterior pituitary gland, which in turn suppresses levels of corticotropin-releasing hormone and corticotropicin, respectively, with a consequent reduction in endogenous cortisol secretion from the adrenal cortex.

Prolonged suppression of corticotropin levels eventually results in atrophy of the adrenal cortex, which may become clinically relevant if the source of exogenous corticosteroid is stopped suddenly, or if there is an acutely stressful event whereby the adrenal cortex is unable to generate an adequate cortisol response (1).

Adrenocortical function can be assessed mainly in two ways, either through screening tests of basal adrenocortical activity, or through dynamic stimulation tests which evaluate impaired adrenal reserve (11). Some of these are more practical than others (Table 3).

Plasma cortisol

The effect of HFA-BDP on the hypothalamic-pituitary-adrenal (HPA)-axis has been addressed in a meta-analysis of AM plasma cortisol effects. Figure 3 shows the regression lines of identity for HFA-BDP and CFC-BDP in which the HFA-BDP data has been extrapolated above the 800 μg day^{-1} dose, because this is the highest dose of HFA-BDP which has been evaluated and represents the maximum licensed dose. As can be seen, there is a dose-response effect for adrenal suppression with both HFA-BDP and CFC-BDP, with no statistical difference between the two lines of identity. Reassuringly, there is no suppression of the mean AM plasma cortisol values up to the maximum dose of 800 μg day^{-1} of HFA-BDP. These results are supported by individual data from Gross et al. and Davies et al. (14,15) (Fig. 4).

In everyday practice it is more relevant to consider individual data rather than mean responses. These data show that even at the highest dose of HFA-BDP (800 μg day^{-1}) less than 5% of the patients showed an abnormally low AM cortisol value (Fig. 4). This would...
TABLE 3. Tests for effect on HPA-axis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Practicality</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 µg ACTH stimulation</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Overnight urinary cortisol</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>24 h urinary cortisol</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>24 h serum cortisol</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>8 AM serum cortisol</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

![Graph showing dose response of % suppression of AM cortisol](image)

Fig. 3. Dose response of % suppression of AM cortisol (meta-analysis of four studies). ●: HFA-BDP (n = 478); ○: CFC-BDP (n = 300).

![Graph showing mean suppression in AM cortisol](image)

Fig. 4. Percentage of patients with AM cortisol values below reference range (week 12). Source: Ref. 17.

suggest that at the doses used in these studies, HFA-BDP has little or no effect on morning plasma cortisol levels and hence, by implication, no effect on the HPA-axis. Indeed, on a µg for µg basis, up to 800 µg, there would seem to be no difference between HFA BDP and CFC BDP in terms of HPA-axis function.

**Urinary cortisol**

In a meta-analysis of 21 studies of urinary cortisol (24 h or overnight) levels, Lipworth (16) showed that fluticasone exhibited a significantly steeper dose-related systemic bioactivity than beclomethasone (1.9-fold; P < 0.05), triamcinolone acetonide (3.7-fold; P < 0.05) or budesonide.

![Graph showing mean suppression in 24 h urinary cortisol](image)

Fig. 5. Dose-response of 24 h or overnight urinary cortisol (meta-analysis of 21 studies). Source: Ref. 16.

![Graph showing effect of HFA-BDP on urinary free cortisol excretion](image)

Fig. 6. Effect of HFA-BDP on urinary free cortisol excretion — percentage change from baseline. Source: Ref. 17.

(4.3-fold; P < 0.001) (Fig. 5), although there were no significant differences between beclomethasone, budesonide or triamcinolone. In the studies analysed, all the inhaled steroids were used within the recommended dosing range (up to 2 mg day⁻¹) and all produced dose-related adrenal suppression.

This dose-response effect on urinary cortisol was also seen by Thompson et al. (17) with HFA-BDP (Fig. 6). In this 14-day, dose level blind, randomized, parallel group study, patients with mild asthma were randomized into five treatment groups (placebo, HFA-BDP 200, 400 and 800 µg day⁻¹; CFC-BDP 800 µg day⁻¹) and the relative effect on 24-h urinary free cortisol (UFC) assessed. As can be seen, there was a shallow dose-dependent fall in 24-h UFC excretion with increasing doses of HFA BDP. The mean percentage change in 24-h UFC excretion with HFA-BDP 200 µg day⁻¹ was not significantly different to that obtained with HFA-placebo, with there being no clinically significant differences at the other HFA-BDP dose levels. In addition, the mean degree of suppression at 800 µg day⁻¹ HFA-BDP was not significantly different than at 800 µg day⁻¹ CFC-BDP (95% CI: -2.16, 47.89%).

**Osteocalcin**

Within bone tissue there is a high degree of metabolic turnover that reflects the dynamic equilibrium between the
activity of the bone-forming cells (osteoclasts) and the breakdown cells (osteoblasts). Bone loss though long-term corticosteroid administration is due to both suppression of bone formation and also to increased bone resorption (due to reduced secretion of sex hormones) together with increased parathyroid activity due to reduced calcium absorption from the bowel and kidneys. Secretion of serum osteocalcin from osteoblasts is thought to be the surrogate marker of choice for assessing bone turnover, due to its sensitivity, specificity and high degree of reproducibility (16).

Whilst there are guidelines on the prevention and treatment of osteoporosis due to oral corticosteroids (18) the relevance to inhaled corticosteroid therapy remains uncertain. However, there are very few controlled studies that have evaluated the effects of inhaled corticosteroids on bone density, and most of these are difficult to interpret because of their relatively small size and the presence of confounding factors (such as previously administered oral corticosteroids). The evidence has been systematically reviewed and it would seem prudent to perform at least one measurement of bone density in at-risk patients receiving high dose inhaled corticosteroid (e.g. postmenopausal women, patients with high alcohol consumption, patients with a familial history of osteoporosis), so as to have a baseline measurement against which to assess treatment effects (16).

With regard to HFA-BDP and bone turnover, Prenner et al. (19) compared the effect of CFC-BDP (400–1600 µg day⁻¹) with HFA-BDP (200–800 µg day⁻¹) over a 12 month period (Fig. 7). During this time there was no significant effect (as assessed by change from baseline in serum osteocalcin) by either beclomethasone formulation, suggesting that, in this case at least, the doses of inhaled corticosteroid used have, reassuringly, no effect on bone turnover. Further longer term studies using bone density measurements are required, however, in at-risk groups.

**Summary**

As has been discussed in the previous sections of the Supplement, the improved physical characteristics of HFA-BDP extrafine aerosol spray allow BDP to be delivered more efficiently into the large, medium and small airways. This improved delivery has allowed the dose of HFA-BDP to be reduced compared to CFC-BDP and budesonide, whilst maintaining equipotency with fluticasone. However, unlike fluticasone, HFA-BDP does not show a propensity for blood or tissue accumulation when administered with a 12-h dosing interval.

Standard tests for assessing effects on the HPA-axis indicate that HFA-BDP extrafine aerosol has a favourable systemic bioactivity profile. Even up to the recommended dose of 800 µg day⁻¹ HFA-BDP (the highest recommended maximum dose), there appear to be no clinically relevant systemic side effects associated with HFA-BDP (Fig. 8).

Thus, viewing the data as a whole, it would seem that, compared to CFC-BDP and alternative inhaled corticosteroids, HFA-BDP in a dose of up to 800 µg day⁻¹ exhibits a favourable therapeutic ratio.

**References**


