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 understanding 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 laboratory 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 Pharmaceuticals, St Paul, MN, U.S.A.) [hydrofluoroalkane-134a beclomethasone dipropionate (HFA-BDP)] in comparison with other anti-asthmatic preparations, by looking at the influence of pharmacokinetic and pharmacological factors, device factors, efficacy factors and safety considerations on this parameter.

Relative efficacy of HFA-BDP

The HFA-BDP dose ratio for equipotent efficacy can be summarized in the following table (Table 1). 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 CFC-pMDI, a result of (a) fluticasone showing twice the level of receptor potency and affinity compared to beclomethasone dipropionate [and its active metabolite beclomethasone-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 turbuhaler, 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 impaction 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>
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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) (3–8) 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).

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**Fig. 1.** Schematic diagram to illustrate intravascular vs. extravascular distribution with steady-state inhaled corticosteroid. FP: fluticasone propionate; 17-BMP: beclomethasone-17-monopropionate.
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 corticotropin, 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).

For example, the most sensitive way to evaluate basal diurnal adrenocortical activity is to perform a 24-h integrated measurement of plasma cortisol levels or urinary free cortisol excretion (11). However, these are impractical in a routine, outpatient environment, and are generally only used in the research laboratory. For this reason more practical methodologies are usually employed, such as the measurement of fractionated overnight or early morning urinary cortisol corrected for creatinine excretion (12,13), which has been shown to be as sensitive as an integrated 24 h urinary free cortisol collection.

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>
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<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>

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

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 beclometasone (1.9-fold; P<0.05), triamcinolone acetonide (3.7-fold; P<0.05) or budesonide

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

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 beclometasone, 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...
FIG. 7. Serum osteocalcin values during a 1-year study (HFA-BDP vs. CFC-BDP). Source: Ref. 19. ---: HFA-BDP (200–800 µg day⁻¹); ---: CFC-BDP (400–1600 µg day⁻¹).

FIG. 8. 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.

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


