Modulite® technology: pharmacodynamic and pharmacokinetic implications

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Abstract In the drive to replace chlorofluorinated hydrocarbons (CFCs) by alternative more environmentally friendly propellants in pressurized metered dose inhalers (pMDIs), Chiesi has developed new inhalers using Modulite® technology. The aim was to obtain CFC-free pMDIs which are equivalent, in terms of safety and efficacy, to the previous CFC devices at the same dose. When beclometasone dipropionate (BDP) and budesonide Modulite® formulations were compared to the equivalent CFC products there was no significant difference in morning serum cortisol or urinary cortisol excretion, at the maximum recommended daily dose (2000 µg or 1600 µg respectively).

Single dose pharmacokinetic studies in both healthy volunteers and asthmatic patients compared systemic exposure (B17MP levels) for BDP-CFC with BDP Modulite® and extrafine BDP-HFA (QVAR®). B17MP levels for BDP-CFC and BDP Modulite® were comparable, but substantially less than that seen with extrafine BDP-HFA.

After 6 weeks of treatment in asthmatic patients, B17MP AUC after inhalation of BDP (1000 µg twice-daily) from BDP Modulite® was comparable with that obtained after BDP-CFC (Becloforte®). Plasma profile of BDP and B17MP were similar after inhalation from BDP Modulite® with standard actuator or delivered via a spacer, suggesting that pulmonary delivery of BDP to the lung is similar with both actuators.

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INTRODUCTION

Inhalation is regarded as the preferred route for the treatment of airways disease because it delivers drugs to the site where they are needed. As a result, reduced doses can be administered, compared with systemic therapy, decreasing the potential for systemic exposure and improving the adverse-event profile. As a means of administering inhaled drugs, the pressurized metered dose inhaler (pMDI), rather than the dry powder inhaler, is currently the device of choice for asthma inhalation therapy. The pMDI is well-established as a safe and reliable delivery system and it is the device most widely used by adults with asthma (1), estimated to comprise around 68% of the total world-wide inhaled drug market.

There are two major classes of inhaled therapy established for the treatment of reversible obstructive airways disease: bronchodilators and anti-inflammatory agents, generally steroids. Beclometasone dipropionate (BDP) and budesonide (BUD) are widely used topically active synthetic glucocorticosteroids. pMDIs containing BDP or BUD with chlorofluorinated hydrocarbon (CFC) propellants (e.g. trichloro and dichlorofluoromethane) have been in use for more than 20 years. In the drive to replace CFCs by alternative more environmentally friendly propellants in pMDIs, Chiesi Farmaceutici has developed new pMDI products using the Modulite® technology. In Modulite® pMDIs, the drug is dissolved in the propellant, HFA134a (Norflurane), with the aid of a co-solvent such as ethanol. The vapour pressure of the propellant, the proportion of co-solvent and the dimensions of the actuator orifice will largely determine the spray pattern from such a formulation. The final particle size distribution then depends on the drug concentration in a droplet and any other non-volatile components, which have been added. The permutation of these factors allows the design of a drug product with a chosen particle size distribution (2). The aim was to obtain hydrofluoroalkane (HFA) products therapeutically equivalent at equal doses in terms of safety and efficacy to the previous CFC devices.

BACKGROUND INFORMATION ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF INHALED BDP AND BUD

It is known that BDP is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to the active metabolite
beclometasone-17-monopropionate (B17MP) (3). The absolute bioavailability following inhalation of the CFC product is approximately 2% and 62% of the nominal dose for unchanged BDP and B17MP respectively (4). Systemic absorption of unchanged BDP occurs mainly through the lungs with negligible oral absorption of the swallowed dose. The systemic absorption of B17MP arises from both lung deposition and oral absorption of the swallowed dose. The bioavailability of orally administered BDP is negligible but pre-systemic conversion to B17MP results in absorption of approximately 40% of the swallowed portion as B17MP. There is an approximately linear increase in systemic exposure with increasing inhaled dose (5). The terminal elimination half-lives are 0.5 hours and 2.7 hours for BDP and B17MP respectively (4).

Plasma protein binding is moderately high; BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues (6). The main product of metabolism is the active metabolite (B17MP). Minor inactive metabolites, beclometasone-21-monopropionate (B21MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure. B17MP metabolite is the most active with approximately 30 times the potency of BDP. B17MP is also the most abundant metabolite in the plasma. Therefore the majority of the systemic corticosteroid effects will be related to B17MP systemic exposure (7).

BUD is a racemic mixture of R and S epimers. In vitro, no inter-conversion between the two epimers has been observed. BUD has a high relative affinity for the glucocorticoid receptor and the R epimer has 2-fold greater affinity than the S epimer (8). BUD is a moderately lipophilic compound that shows a rapid uptake into the airway mucosa. Although topical BUD is rapidly and extensively absorbed through the lung, there is no evidence of intrapulmonary drug metabolism apart from conjugation with fatty acids. In vitro tests did not demonstrate any oxidative or reductive metabolism of BUD by human lung homogenate. Budesonide is metabolized by cytochrome P450 3A4 in human liver (9). Elimination half-life was about 2-7 hours for both epimers after intravenous administration and a similar elimination half-life was observed after inhalation route. The oral bioavailability of BUD was about 10%, with approximately 90% of the dose subject to first pass metabolism in the liver (8).

There is an approximately linear increase in systemic exposure with increasing inhaled dose from 400 to 1600 μg (10). BUD systemic absorption arises from both lung deposition, that may vary from 10 to 30% depending on the device and user technique, and oral absorption of the swallowed dose.

The systemic pharmacodynamic effects of BDP and its metabolites and BUD can be assessed by measuring the hypothalamus-pituitary adrenal (HPA) function that is a biomarker of the systemic activity of any exogenous corticosteroid, including those taken by inhalation. It has been well documented that doses up to 400 μg BDP in adults have no measurable effect on endogenous cortisol levels. The maximum recommended dose of BDP (2000 μg) does show reductions in endogenous cortisol of approximately 40% in healthy volunteers (5). Doses up to 400 μg day⁻¹ of BUD via Turbuhaler® have no measurable effect on endogenous cortisol levels in adult asthmatic patients (11) while a minimal systemic effect on plasma cortisol (12) has been observed at 800 μg day⁻¹; at 1600 μg day⁻¹, the maximum BUD adult dose, a transient reduction in endogenous cortisol of approximately 20% in asthmatic patients (11) and of 41% in healthy volunteers (12) was observed.

**SYSTEMIC PHARMACODYNAMIC EFFECTS OF MODULITE® FORMULATIONS**

The effect of BDP Modulite® on the HPA axis has been compared with BDP-CFC (Becloforte®, GSK) 2000 μg (8 × 250 μg) in a crossover study conducted in 12 healthy volunteers (13).

There was a similar reduction in serum cortisol (about 40% decrease) and in urinary cortisol excretion (45% decrease), for both treatments (Figure 1).

In a separate study, extrafine BDP-HFA (Bectazone®, Baker Norton) showed significantly greater 24h cortisol suppression than BDP-CFC (Becloforte®, GSK) after a single 2000 μg dose (5).

The relative effect of BUD Modulite® on the HPA axis has been compared with that of currently available BUD inhalers products, Pulmicort® CFC pMDI (BUD-CFC) and Pulmicort Turbuhaler® (BUD-DPI) (Astra-Zeneca), in a three-way crossover, single dose study in 12 mild asthmatic patients (14).

No difference in the serum cortisol concentration versus time curves (Figure 2), or in the urinary cortisol excretion between the three different BUD formulations has been observed.

**DOES PHARMACEUTICAL DATA PREDICT THE SAFETY PROFILE? DATA FROM VOLUNTEERS**

In vitro characterization of aerosol formulations normally with Andersen Cascade Impactor (ACI) is important in guiding pharmaceutical product development and is used in final quality control. The efficiency of delivery to the lung is dependent on particle size. It is generally agreed that particles below 4.7 μm reach the lungs while larger particles will deposit in the mouth and are swallowed (15,16).
MODULITE®: PK/PD IMPLICATIONS

Cortisol in serum

Normalized cortisol excretion in urine

The central line in each box represents the median value; the upper and the lower lines represent the 75th and the 25th percentiles.
The bars represent the minimum and maximum values.

**FIGURE 1.** Mean serum cortisol profile and urinary excretion (normalized for urinary creatinine) in healthy volunteers (n=12) after inhalation of a single 2000 μg dose of BDP Modulite® and BDP-CFC.

**FIGURE 2.** Mean serum cortisol profile in mild asthmatic patients (n=17) after inhalation of a single 1600 μg dose of R I I D Modulite®, BUD-CFC and BUD-DPI.

**BDP**

Twelve healthy volunteers were enrolled into a single 1000 μg dose, three-way crossover, pharmacokinetic study of three different BDP pMDI formulations: BDP Modulite® with spacer (Jet®) (Beclojet® 250), MMAD (mean mass aerodynamic diameter) 2.6 μm, extrafine BDP-HFA (QVAR® 100, 3M Pharmaceuticals) MMAD 1.2 μm, Chiesi BDP-CFC with spacer (Jet®) (Clenil Forte® 250) MMAD 4.7 μm (17) (Figure 3).

The area under the concentration-time curve (AUC) for BDP and its metabolite B17MP were assessed following inhalation from each pMDI product. The AUC calculated for B17MP during the first hour after inhalation AUC(0-1h) and BDP AUC(0-τ) (calculated up to the last measurable plasma concentration) were likely to reflect lung rather than gut absorption, since BDP is rapidly metabolized to B17MP in the lung. The AUCs for BDP and B17MP were significantly greater with the extrafine BDP-HFA formulation than with the BDP-CFC and BDP Modulite® Jet® formulations (Figure 4).

BDP from the extrafine BDP-HFA pMDI was more rapidly absorbed into the systemic circulation as shown by B17MP AUC(0-1h). The change in MMAD from 4.7 μm to 2.6 μm had a negligible influence on BDP absorption, with AUCs for BDP and B17MP only slightly increased, while the change in MMAD from 2.6 μm to 1.2 μm was associated with a marked increase in absorption.

A relationship was seen between the amount deposited in the ACI stages 3 to 6 (aerodynamic diameter between 4.7 and 0.7 μm) and AUCs (Figure 5). The in vitro and pharmacokinetic data suggest that from the safety viewpoint the transition from BDP-CFC to BDP Modulite® can occur without any dose adjustment.

**BUD**

The systemic exposure to BUD epimers, following a single inhalation of 1600 μg (8 x 200 μg shot⁻¹), from two BUD Modulite® pMDIs with different orifice diameter (0.30 and 0.42 mm) was assessed in six healthy volunteers (18). The fine particle dose (FPD < 4.7 μm) for both epimers is higher with the 0.30 mm compared with the 0.42 mm orifice (29.1 vs. 16.8 μg for epimer R,
and 19.7 vs. 11.4 μg for epimer S respectively) and the MMAD was slightly lower with the smaller orifice (3.1 μm, vs. 3.5 μm) (Figure 6).

BUD plasma levels peak immediately after administration and reflect mainly lung absorption. Overall BUD bioavailability was 30% (S epimer) and 40% (R epimer) higher using the actuator with the smaller orifice, suggesting that an increase in the FPD increases the peripheral lung deposition with consequent higher systemic absorption. However, absorption rate and elimination half-life were unaffected by the change in the orifice diameter with the exception of a slightly reduced elimination half-life of S epimer (Figure 7).

The choice of a different actuator orifice allows modulation of the fine particle dose to provide Modulite® HFA pMDIs matching different marketed BUD inhalers.

**SYSTEMIC EXPOSURE IN PATIENTS**

The pharmacokinetics of BDP after inhalation from BDP Modulite® have been compared with a reference
BDP-CFC product (Becloforte®, GSK) in adult patients with moderate-to-severe persistent asthma (19). Thirty-two adult patients with moderate/severe asthma entered a double-blind, double-dummy, randomized, parallel-group study. They were randomly assigned to 2000 µg BDP daily (1000 µg twice-daily) from either BDP Modulite® or BDP-CFC both inhaled via a spacer device (Volumatic®, GSK). Pharmacokinetic sampling was carried out after 6 weeks of treatment following the last morning administration. Twenty-eight patients (13 male and 15 female) completed the pharmacokinetic study. Unchanged BDP plasma levels were very low, and below the detection limit shortly after inhalation; therefore the pharmacokinetic evaluation was performed for the active B17MP metabolite only. The total systemic exposure to B17MP represented by the plasma AUC over the dosing interval (AUC,) at steady-state in asthmatic patients, after inhalation of BDP (1000 µg twice-daily) from BDP Modulite® (AUC,: 2124 pg ml⁻¹ h) was comparable with that obtained after BDP-CFC (AUC,: 2160 pg ml⁻¹ h). The small difference observed in the initial absorption rate for B17MP with a higher Cmax and an earlier Tmax with BDP Modulite® appears to be due to a rapid initial absorption rate from the lung, rather than a difference in pulmonary deposition, since the plasma AUC values are comparable (AUC,: ratio: 0.98) (Figure 8).

The difference in Cmax observed for the Modulite® product is unlikely to result in differential pharmacological effects, since the systemic effects of corticosteroids (such as HPA axis suppression) are correlated with the total systemic exposure rather than peak concentrations (20). In contrast to these findings, the AUC and Cmax for B17MP obtained with both extrafine HFA formulations of BDP (QVAR® and Beclazone®) have been reported to be between two and three times higher than the CFC reference product (5,21).

**INFLUENCE OF CHARCOAL BLOCK AND OF A SPACER DEVICE ON PULMONARY DEPOSITION AND SYSTEMIC EXPOSURE**

The effects of a charcoal block and the use of the spacer (Jet®) on the absorption of BDP and B17MP after BDP Modulite® have been studied in six healthy subjects after inhalation of a single dose of BDP (1600 µg), using a crossover design (22). BDP and B17MP plasma levels were determined over a 12 hours period. The charcoal block did not affect the plasma levels of BDP, confirming that BDP found in the systemic circulation arises almost entirely from BDP absorbed unchanged from the lung, and that swallowed BDP is not bioavailable due to the pre-systemic conversion to B17MP. As regards B17MP plasma levels, these were only slightly reduced (less than 20%) by the charcoal block, confirming that the pulmonary absorption is the main source of systemic exposure to B17MP. The BDP and B17MP plasma profiles after inhalation from BDP Modulite® with standard actuator or from the same formulation delivered via the spacer were virtually
identical, suggesting that pulmonary delivery of BDP to the lung is similar with and without spacer (Figure 9).

**CONCLUSIONS**

The Modulite® formulations of inhaled steroids in HFA are equivalent, in term of safety, to the marketed (CFC and DPI) inhalers. The extent of cortisol suppression evaluated in healthy volunteers and patients using the maximum recommended dose (2000 μg BDP and 1600 μg BUD) was comparable for both corticosteroids. The similarity of the systemic pharmacodynamic effects produced by the products is consistent with the in-vitro data.

By combining Modulite® formulations with different orifice diameters, it has been possible to manipulate the fine particle dose so that they closely match currently available inhalers.

Systemic exposure for Modulite® formulations are comparable with CFC products at the same dose. Pharmacokinetic studies performed, in both healthy volunteers and in asthmatic patients, using the standard actuator and an actuator incorporating a spacer demonstrated that the systemic exposure was comparable for Modulite® inhaler and CFC inhaler.

Systemic exposure of BDP Modulite® is substantially less than for the extrafine BDP-HFA pMDI (QVAR® 3M) for which an adjustment of the dose is required.

After BDP Modulite® inhalation, the systemic exposure of BDP is unaffected by the spacer device and only slightly reduced by the charcoal block, confirming the optimal lung deposition of the corticosteroid.

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