



Comparative physicochemical and pharmacokinetic profiles of inhaled beclomethasone dipropionate and budesonide

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Introduction

The development of corticosteroids deliverable by inhalation represented a major step forward in the treatment of asthma. The optimal features of a corticosteroid intended for inhalation are low water solubility (to maximize time spent in the lung), high receptor affinity (potency) and a short half-life in the systemic circulation (to minimize systemic adverse effects). This article will review the extent to which beclomethasone dipropionate (BDP) and budesonide meet these criteria.

Structure-activity Relationships

A C1-C2 double bond in a corticosteroid molecule enhances glucocorticoid activity and reduces mineralocorticoid activity. BDP is a 17 α ,21-diester with a chlorine atom in the 9 α position (1). Budesonide is a 16 α ,17 α -acetol-substituted molecule that does not contain a halogen atom. Budesonide is an equal mixture of two epimers designated 22*R* and 22*S*. The chemical structures of BDP and budesonide, and their primary metabolites, are provided in Figure 1.

RECEPTOR AFFINITY

Receptor affinity is a measure of how strongly the active molecule binds to the intracellular glucocorticoid receptor, and it is related closely to the anti-inflammatory activity of the compound. High affinity of the compound for the glucocorticoid receptor will result in greater changes in the regulation of gene transcription and gene products, which will lead to modulation of inflammatory processes. When applied

topically, budesonide demonstrates greater potency than BDP, based on the human skin vasoconstriction assay (2), with 22*R*-budesonide having 2-3 times the vasoconstricting potency of the 22*S* epimer (1). However, it has been recognized that this test may be unreliable for predicting clinical efficacy in the lungs. Indeed, although budesonide has 2-3 times better skin-blanching properties than BDP, numerous clinical studies in asthma treatment have shown that the two drugs have equivalent efficacy when administered at the same dose via the same type of delivery device.

Rohdewald *et al.* (3) determined the receptor affinities of inhaled glucocorticoids by performing *in vitro* competition assays using human lung cytosol. Receptor affinities of the two drugs and the metabolites of BDP [expressed relative to dexamethasone (100), with a high number indicating high affinity] are shown in Table 1. They found that BDP has a relative receptor affinity 20-fold less than that of budesonide. However, the relative receptor affinity of 17-beclomethasone monopropionate (17-BMP), one of the compounds to which BDP is transformed in the lung, is slightly greater (about 1.5 times) than that of budesonide. This suggests that the metabolism of BDP to 17-BMP is actually an activation step, rather than a deactivation step (as previously thought), and results in a compound with similar affinity to budesonide for the glucocorticoid receptor. 21-BMP has low affinity for the glucocorticoid receptor, as do the metabolites of budesonide.

WATER SOLUBILITY

Rohdewald *et al.* (3) also showed that BDP is poorly water soluble. The rate at which a compound dissolves in the aqueous mucous layer of the bronchial mucosa is believed to be the controlling factor for its systemic absorption. Budesonide and 17-BMP have approximately the same water solubility and both are more water soluble than BDP (3). The 22*R* epimer of budesonide is less water soluble than the 22*S* epimer (4,5).

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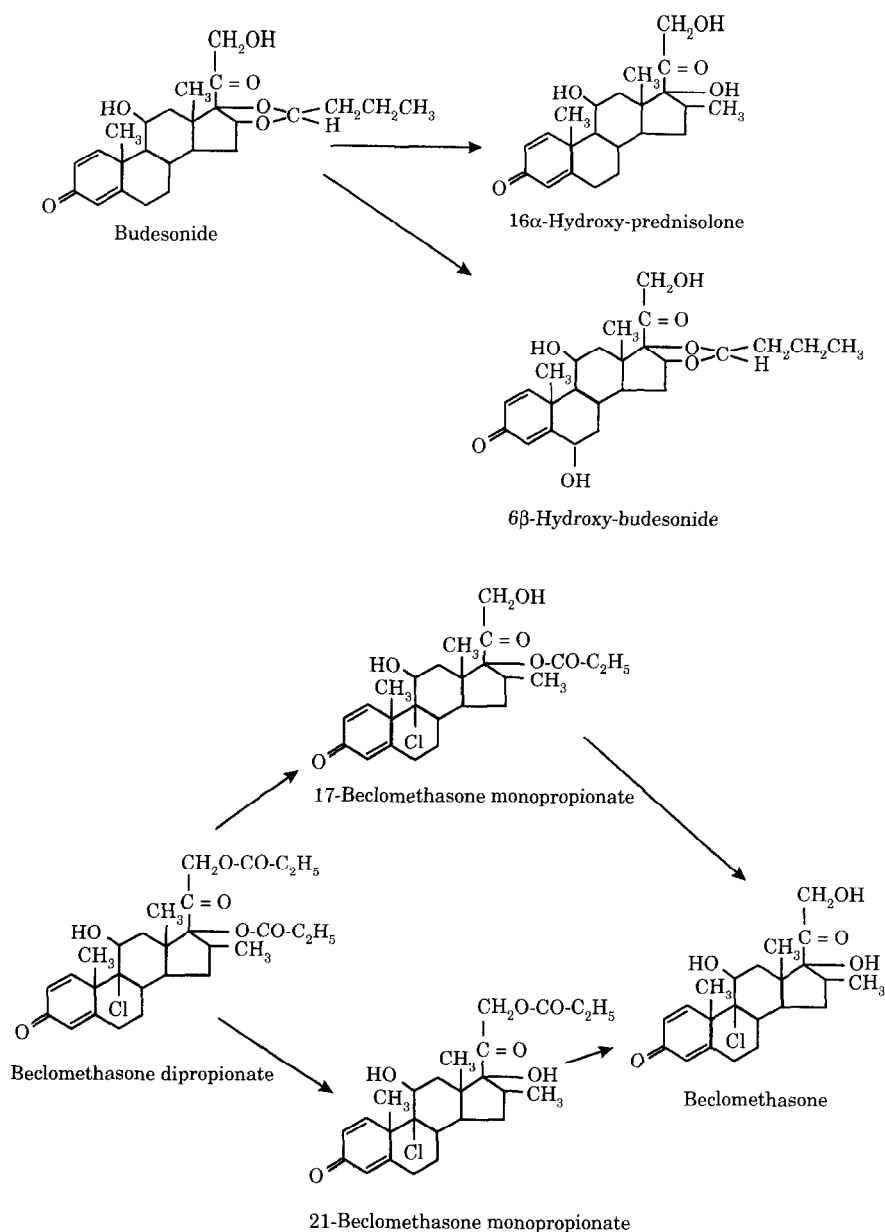


FIG. 1. Chemical structures and primary metabolic pathways of BDP and budesonide.

However, although budesonide diffuses into the plasma, the appearance of 17-BMP in plasma is limited by the rate of hydrolysis of BDP, which in turn is dependent on its speed of dissolution. BDP may therefore form a reservoir in the lung which can be converted locally to the highly active 17-BMP. Similarly, the formation of fatty acid esters of budesonide in the lung, which can be readily hydrolysed, may provide for maintenance of the active substance in pulmonary tissues (6).

One disadvantage of the poor water solubility of BDP is that the dosage that can be formulated for a nebulizer is lower than that for budesonide (50 $\mu\text{g ml}^{-1}$ suspension vs. 250 $\mu\text{g ml}^{-1}$ suspension, respectively) (1).

However, the use of nebulizers has been declining because it has been discovered that a metered dose inhaler (MDI) plus a spacer device, with or without a mask attachment, is a more efficient delivery device (see below) and can be substituted for a nebulizer in most situations (7-9).

Pharmacokinetic Properties

ABSORPTION AND DISTRIBUTION

The majority of the dose of a corticosteroid administered by inhalation does not reach the desired target

TABLE 1. Relative receptor affinities (compared with dexamethasone) of beclomethasone dipropionate, and its metabolites, and budesonide at the glucocorticoid receptor. Data from Ref. 3

Compound	Relative receptor affinity ^a
Dexamethasone	100
BDP	43
17-Beclomethasone monopropionate (17-BMP)	1345
21-Beclomethasone monopropionate (21-BMP)	0.9
Beclomethasone	76
Budesonide	935
6 β -Hydroxy-budesonide	6
16 α -Hydroxy-prednisolone	3

^aThe higher the number the greater the affinity for the glucocorticoid receptor.

site of the lungs, the actual percentage varying between about 10% and 20% depending on the delivery device used. No hydrolysis or degradation of BDP was observed in artificial gastric juice over a 3 h period (10), whereas rapid hydrolysis to 17-BMP occurred in artificial intestinal fluid. This suggests that swallowed BDP probably passes through the stomach unchanged but is then almost completely hydrolysed to 17-BMP in the intestine, epithelial cells, blood or liver. Therefore, it is likely that the majority of BDP that is ingested enters the systemic circulation as 17-BMP, with only small amounts of BDP being absorbed. It has been estimated that 70% of BDP that has been ingested is subject to pre-systemic metabolism (11). Large variations have been reported in the time to maximum plasma concentration (T_{max}) of BDP following inhalation. In 12 healthy male volunteers receiving BDP 2000 μ g by inhalation, peak plasma concentrations of BDP (1275 pg ml^{-1}) and 17-BMP (1364 pg ml^{-1}) were observed within 5 min and 3 h, respectively (12). In 23 patients with mild asthma inhaling BDP 400 μ g formulated with a chlorofluorocarbon (CFC) propellant or BDP 200 μ g with a CFC-free propellant, T_{max} occurred in 120 min and 36 min, respectively, with similar peak plasma concentrations being achieved (41 vs. 34 pg ml^{-1}) (13,14).

Of the budesonide that is ingested, between 10% and 13% is bioavailable, with approximately 90% subject to pre-systemic metabolism (4). The pharmacokinetic profiles of the two epimers are broadly similar (4,5). Following inhalation, peak plasma concentrations of budesonide are achieved within 1 h (4). Systemic budesonide is 88% plasma protein bound (4) and has a large volume of distribution, approximately 300 l (4,5,15). 22*R*-budesonide has a larger volume of distribution than the 22*S* epimer (424 l and 245 l, respectively), because it is more lipophilic (4,5).

Similar volumes of distribution for budesonide have been found in children with asthma, 4.8 l kg^{-1} for the 22*R* epimer compared with 3.1 l kg^{-1} for the 22*S* epimer (16). After inhalation of a single dose of budesonide 1600 μ g, the average concentration of the steroid in the lung tissue of 11 patients undergoing thoracotomy 1.5–4 h later was 2386 pg ml^{-1} (17,18). The corresponding plasma concentration was 271 pg ml^{-1} .

METABOLISM AND ELIMINATION

Both BDP and budesonide are inactivated predominantly by the liver. BDP is hydrolysed to 17-BMP and 21-BMP, in the lung and the liver. Wurthwein and Rohdewald (10) showed that BDP is transformed only slowly and incompletely to 17-BMP when incubated with bronchial secretions *in vitro*. However, when incubated with human lung tissue, BDP was rapidly hydrolysed (half-life 10 min) to 17-BMP. This suggests that hydrolysis of BDP commences at first contact with the bronchial secretions but occurs considerably faster in the presence of esterases following absorption into lung cells. 17-BMP is highly stable in lung tissue (half-life 12 h). Once in the plasma, there is some inactivation of 17-BMP by ester interchange to 21-BMP. However, this is slow compared with the metabolic activity of human liver. Andersson and Ryrfeldt (19) found that BDP was immediately hydrolysed to BMP (both 17- and 21-BMP) in the liver, which was either hydrolysed to beclomethasone or biotransformed by oxidative and reductive pathways to unknown inactive metabolites with short half-lives of 15–30 min. These metabolites are excreted either into the bile or in the faeces. Jenner and Kirkham (20) have shown that the plasma elimination half-lives of BDP and 17-BMP are 30 and 37 min, respectively, after intravenous administration of 1 mg of radiolabelled BDP. In contrast, in

TABLE 2. Pharmacokinetic parameters of budesonide, beclomethasone dipropionate (BDP) and its active metabolite 17-beclomethasone monopropionate (17-BMP). Data from Refs 3–5,11,12,19

	Budesonide	BDP	17-BMP
Oral bioavailability	~ 10%	~ 30%	NA
Volume of distribution	301 l	NA	NA
Plasma clearance	84 l h ⁻¹	NA	NA
Half-life after IV administration	120–180 min	30 min	37 min

IV, intravenous; NA, not available.

12 volunteers, Falcoz *et al.* (12) reported mean plasma elimination half-lives of 6 min and 6.5 h for BDP and 17-BMP, respectively, after inhalation of BDP 2000 µg.

Budesonide, unlike BDP, is not biotransformed in the lung or gastrointestinal tract (2). In the liver, budesonide is metabolized primarily via oxidative and, to a much lesser extent, reductive pathways to six metabolites, primarily 16 α -hydroxy-prednisolone and 6 β -hydroxy-budesonide (21,22). These metabolites are the products of the inducible form of cytochrome P450, CYP3A4 (18), and have similar half-lives to the parent compound but are relatively inactive (50- to 200-fold less active than budesonide) (4). Hepatic metabolism of budesonide occurs 2–4 times faster than that of either 17-BMP or 21-BMP (4,19). Total plasma clearance of unchanged budesonide is 84 l h⁻¹ and is 117 and 68 l h⁻¹ for the 22*R* and 22*S* epimers, respectively (4).

As mentioned earlier, it is desirable that an inhaled corticosteroid has a short half-life in plasma. The half-life of unchanged budesonide following both inhalation and intravenous administration to healthy volunteers has been reported to be between 2 and 3 h (4).

The important pharmacokinetic parameters of BDP and its active metabolite 17-BMP, and of budesonide are summarized in Table 2.

Delivery Devices

The method by which an inhaled medication is delivered will obviously influence its lung deposition characteristics. Selroos *et al.* (23) have performed a comprehensive comparison of delivery devices (excluding nebulizers) for inhaled asthma medication. At present, the MDI is the most widely used device. Typically, 10–15% of a dose from an MDI is deposited in the lungs. The use of a spacer device attached to an MDI approximately doubles the percentage of drug reaching the lungs. Drug deposition from a dry powder inhaler is similar to that from an MDI whereas delivery from a breath-actuated device is between 20% and 35%, depending on the drug. Deposition from the newer CFC-free MDIs containing BDP appears to be

substantially greater than that from the conventional BDP MDI (13,24). With a nebulizer, only approximately 10% of the total dose reaches the lungs, with the majority of the drug being lost in the apparatus, to the air, or exhaled (25).

The higher the percentage of the total drug dosage that reaches the lungs, the greater the local clinical efficacy. At the same time, the lower the percentage of extrapulmonary deposition, the lower the risk of oropharyngeal and, possibly, systemic adverse effects. Inter- and intraindividual differences in device technique can also have an impact on drug deposition.

The various delivery devices also differ regarding their ease of use, portability, association with local adverse effects (such as inhaler-induced cough) and cost, and all of these factors should be considered in combination with the patient's requirements when inhaled corticosteroid therapy is initiated (26,27). Efforts must be made to ensure that the patient is capable of correctly and consistently performing all steps associated with proper use of the particular device, and technique should be reassessed periodically (28). Pedersen (27) has reviewed the advantages and limitations of the various delivery devices. A nebulizer is the appropriate device for children <6 months of age (28,29). It should be possible to use an MDI plus spacer with a fitted infant facemask for children aged between 6 months and 1 year. An MDI plus spacer with mask is suitable for children aged 1–5 years (27,28). Children aged ≥ 5 years are often able to use a dry powder inhaler; those aged >7 years should be able to use a breath-actuated device or an MDI plus spacer without a mask (27). An MDI plus spacer, breath-actuated device or dry powder device is preferable for elderly or other individuals who have difficulty co-ordinating inspiration and device actuation. The area of delivery devices will continue to evolve as new CFC-free inhalers are introduced over the next few years and new spacer devices are developed. Additional research comparing the different types of delivery devices is required, as are studies determining which devices are most suitable for which patients.

Summary

The physicochemical and pharmacokinetic characteristics of BDP and budesonide are somewhat different, but the overall result is that both are well suited for use as inhaled corticosteroids. Both BDP and budesonide are metabolized primarily by the liver, with one of the metabolites of BDP, 17-BMP, having greater receptor affinity than either the parent compound or budesonide, which has no active metabolites. BDP has a lower water solubility than either 17-BMP or budesonide, which have similar water solubilities. Budesonide has lower oral bioavailability than BDP; however, it is generally reported to have a longer plasma half-life than either BDP or 17-BMP. The physicochemical and pharmacokinetic profiles of inhaled BDP and budesonide provide both compounds with a favourable ratio of topical to systemic effects and support their well-established role in the treatment of asthma. The device used to deliver an inhaled corticosteroid influences the lung deposition of the drug and selection of the device should be made with an understanding of the particular advantages and disadvantages of the device for each individual patient.

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