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Pharmacological Factors that Influence the Choice of Inhaled Corticosteroids

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Abstract

Local therapeutic effect relative to the risk of adverse effects of inhaled drugs, i.e. airway selectivity, is determined by the efficiency of the delivery system and the physicochemical and pharmacokinetic properties of the drug molecule. For the inhaled corticosteroid formulations, many of the pharmacokinetic prerequisites for airway selectivity have been fulfilled, but there are still differences that may influence the choice of treatment regimens. This choice should be based on disease severity, age, inhalation technique, preference and expected compliance, together with a knowledge of individual features of different corticosteroid formulations.

Simple to use, hand-held pressurised or breath-actuated inhalers have favourable lung deposition properties and are appropriate for most patients. For small children or severely ill patients, nebulised treatment or spacers may be advocated. A corticosteroid formulation with a high intrinsic activity and long duration of action allows for once-daily administration in some patient groups. These properties may also partly compensate for noncompliance when more frequent administration schemes are used. The risk of adverse effects is reduced if systemic exposure is held to a minimum by rapid elimination and low tissue distribution.

Corticosteroids are currently the most efficient anti-inflammatory therapy in asthma. An understanding of the pharmacokinetic and pharmacodynamic differences between different inhaled corticosteroid formulations allows for individualised treatment and improved therapeutic outcome. This overview will detail the pharmacological factors governing clinical efficacy and safety, and discuss differences between available corticosteroid formulations.

In pharmacological doses, in addition to their endocrine action, corticosteroids affect most components of the inflammatory cascade. These effects are mediated via common pathways involving intracellular binding to specific receptors and subsequent interaction with the genome, either directly or via transcription factors.[1] Glucocorticoid receptors appear to be present in all eukaryotic cells, and attempts to develop corticosteroids with a selective intracellular action on the inflammatory but not endocrine processes have so far been unsuccessful. Since local adverse effects are generally negligible, research has instead been focused on the development of corticosteroids with high (but nonspecific) intracellular action that are targeted to the site of the inflammatory lesion by local delivery.

The airway selectivity of an inhaled corticosteroid formulation is due to a combination of high topical activity and low systemic effects, and is determined by the properties of the delivery system and the corticosteroid in combination (table I). Topical activity depends on the amount of drug that is actually delivered to the target tissue,

Table I. Pharmacokinetic factors influencing the airway selectivity of inhaled corticosteroids

Delivery system factors	Corticosteroid factors
Lung (factors that maximise topical activity)	
High deposition	High intrinsic activity
	High airway binding
Rest of body (factors that minimise systemic effects)	
Low gastrointestinal deposition	Rapid systemic elimination
	Low oral availability
	Low tissue retention

the 'intrinsic' activity of the corticosteroid molecule and the local pharmacokinetics of the molecule in the target tissue. The systemic effect is related to the systemic exposure, which depends upon the total amount of the corticosteroid that is absorbed from the airways and the gut, i.e. the total systemic availability, and the elimination of pharmacologically active corticosteroid from the body. The rate of elimination, in turn, depends on the rate of metabolic inactivation, the extent of first-pass metabolism and the tissue distribution.

1. Inhaler Devices

The choice of inhalation device is critical for optimal asthma treatment. Although compliance is improved by a once-daily regimen, a corticosteroid formulation that is difficult to use and has unreliable delivery characteristics is not suitable for once-daily use, since optimal and reproducible drug delivery then becomes even more critical than when the patient is following a treatment scheme with more frequent administration. An ideal inhaler should deposit a large fraction of the delivered dose to the lungs with little variability, and it should be robust, easy to use and preferred by patients of different ages and with different disease severities.

1.1 Fine Particle Dose

Drug delivery to the lungs from an inhaler is critically dependent upon the fine particle dose the inhaler is capable of generating. A particle size of approximately 5μm has been established as the cut-off diameter for appropriate airway deposition. The fraction of the delivered dose consisting of respirable fine particles is a unique feature of each drug/delivery combination rather than the type of device [pressurised metered dose inhaler (pMDI), nebuliser or dry powder inhaler (DPI)], or the pMDI propellant [chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA)]. Hence, although the fine particle fraction generated by a budesonide Turbuhaler® is almost 4 times that with a fluticasone propionate Diskhaler™ at the same nominal dose (40 *vs* 10%, respectively, of the metered dose), the fine particle fraction generated by a budesonide CFC pMDI is about half that with a fluticasone propionate pMDI (20 *vs* 34%).[2] Beclomethasone dipropionate in an HFA pMDI solution has a markedly greater fine particle fraction than beclomethasone dipropionate in various CFC pMDI suspensions (56 *vs* 23 to 34% of exactuator dose <4.7μm).[3] Nebulisers, of which jet nebulisers are the most commonly used for local corticosteroid treatment, are relatively inefficient in the generation of fine particles, and the fraction of the nominal dose generated as fine particles does generally not exceed 10%.[4]

1.2 Lung Deposition

The therapeutic effect of an inhaled anti-asthma drug formulation is linked to the amount deposited in the lungs. This has been clearly shown for both β-agonists[5,6] and ipratropium bromide.[7] In addition, the fraction that is not deposited in and absorbed from the airways will eventually be swallowed, which will reduce the airway selectivity of an orally available corticosteroid. This is especially true for inhalers with less efficient lung delivery: although more than 40% of the systemically available budesonide after inhalation via a pMDI (without mouthwash) was derived from swallowed drug, the corresponding figure for Turbuhaler® (without mouthwash) was 15%.[8] As mouthwash is advocated for all inhaled corticosteroids to avoid local and systemic adverse effects, the oral contribution will be further reduced.

Lung deposition varies greatly for different inhaled corticosteroid formulations (table II). It is also evident that spacer devices not only reduce the

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amount of corticosteroid swallowed, but may also profoundly increase lung deposition. Most lung deposition studies have been performed in healthy individuals under optimal conditions, but the results appear not to differ markedly from those of patients with asthma if the inhalation technique is accurate.[9,14] A more central deposition was, however, implied in patients with asthma than in healthy individuals.[15] Currently, pMDIs are being reformulated with the more environmentally friendly HFA propellant, and although these pharmaceutical efforts have been associated with problems, it appears that lung deposition has been increased.

The use of nebulised corticosteroids is increasing, and is considered to be a convenient alternative in severely ill patients and for young children, patient groups where inhalation technique may be suboptimal. Although systemic exposure (defined as area under the plasma concentration-time curve of budesonide/mg nominal dose) of nebulised budesonide is the same in small children as in adults, lung deposition differs. In children aged 3 to 6 years, lung deposition was 26% of dose delivered to the individual *vs* 58% in adults when budesonide inhalation suspension was delivered via a Pari LC-Jet Plus nebuliser.[11,16] In general, the output from a nebuliser is less than for other inhaler devices and, in both groups of patients, about 50% of the dose was retained in the device and 25% was released into the ambient air.

Similarly, in children aged 2 to 3 years using budesonide pMDI with a spacer connected to a face mask, systemic exposure was the same as in older children (4 to 6 years) and adults who were using a mouthpiece connected to the spacer.[17] These results again imply a reduction in lung deposition with reduced age, as the reduced body size would otherwise lead to elevated plasma concentrations. One consequence of these findings, whether budesonide was delivered via a nebuliser or via a pMDI with a spacer, is that dosage reduction for safety reasons is probably not necessary in small children. However, the reduced lung deposition in small children may reduce the likelihood of a maximum therapeutic effect at a given dose, which may reduce the airway selectivity when compared with that of adults. For budesonide, this is, however, partly compensated for by a higher systemic clearance and lower oral availability in children than in adults.[16,18]

Table II. Lung deposition of inhaled corticosteroids. Data are presented as percentages of metered and delivered doses, where delivered dose = dose received by the subject and metered dose = delivered dose + dose retained in the device

Drug, propellant, device	Deposition (%) of		Reference
	delivered dose	metered dose	
BDP CFC	4	3[a]	9
BDP HFA	56	40[a]	9
Budesonide CFC	16[a]	15	8
Budesonide CFC Nebuhaler™	76[a]	34	10
Budesonide nebulising suspension with Pari LC-Jet Plus nebuliser	58[a]	14	11
Flunisolide CFC	20[a]	17	12
Flunisolide HFA	27[a]	23	12
Flunisolide HFA Aerohaler™	73[a]	40	12
FP CFC		25[b]	13
FP HFA		28[b]	13
Budesonide Turbuhaler®		32	8
FP Diskhaler®		11[a,b]	13
FP Accuhaler®/Diskus®		16[a,b]	13

a Calculated using estimates of retained dose.

b Systemic availability versus nominal dose.

BDP = beclomethasone dipropionate; **CFC** = chlorofluorocarbon; **FP** = fluticasone propionate; **HFA** = hydrofluoroalkane.

1.3 Inhalation Technique

Several studies have shown that more than two-thirds of patients do not manage to handle a pMDI device accurately, even with appropriate instructions and the use of a spacer.[19,20] Additional negative features of pMDIs include the use of broncho-irritating lubricants required for appropriate valve function, environmentally noxious propellants, oropharyngeal impaction because of very high initial plume speed, and dependency of aerosol cloud characteristics upon ambient temperature. Neglecting to shake the canister before use can reduce the lung deposition by half.[10]

With nebulisers, inhalation technique is also critical, and inspiratory flow, tidal volume and the

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duty cycle (i.e. the proportion of inspiration time versus the full breathing cycle time) affects the amount that will be deposited in the lungs.[21] A face mask may be preferred for very young children, but leakage and nasal breathing will make delivery to the lungs unpredictable. In addition, the time required for nebulisation of a single dose, 5 to 15 minutes, reduces convenience and may affect compliance.

Breath-actuated DPIs are generally the most convenient systems for drug delivery to the airways, and preferred by many patients over pMDIs.[22] The deep and forceful breath required to properly deliver a dose from Turbuhaler® is achieved by almost 100% of patients above the age of 8 years,[23,24] and by 37 of 38 patients aged 3 to 6 years.[23] Even in patients admitted to the ward for an acute asthma exacerbation [mean forced expiratory volume in 1 second (FEV_1) at admittance 1.2 L/min], 97 of 99 patients generated a peak flow through Turbuhaler® sufficient for appropriate performance (>30 L/min).[25]

For reliable treatment, intraindividual variability in lung deposition should be as little as possible. This is probably even more important when the patient follows a once-daily treatment regimen. Although Turbuhaler® shows a slightly greater variability in *in vitro* fine particle dose delivery than pMDIs, the variability within and between patients in lung deposition is less with Turbuhaler® than with the pMDI. Even under laboratory conditions where all participants followed instructions for optimal inhalation, variability was halved with Turbuhaler® compared with a pMDI.[8,26] It is likely that these differences are even more pronounced in the clinical situation in favour of the more easy to handle breath-actuated DPIs.

2. Absorption and Intrinsic Activity

Water solubility differs between different inhaled corticosteroids.[27] Although budesonide, flunisolide, triamcinolone acetonide and beclomethasone monopropionate have about the same water solubility (about 10 to 100 mg/L), beclomethasone dipropionate and fluticasone propionate are more lipophilic (water solubility about 0.1 mg/L). Hence, a clinically relevant dose of fluticasone propionate or beclomethasone dipropionate (200μg) requires at least 2L of water to be dissolved, whereas the same amount of a less lipophilic corticosteroid, such as budesonide, would need only 15ml. Pharmacokinetic studies in humans have shown that budesonide is readily dissolved in human bronchial secretion,[28] and is rapidly absorbed after oral inhalation [time to maximum concentration (t_{max}) after oral inhalation via Turbuhaler® is about 20 minutes, mean absorption time about 40 minutes].[29] In contrast, fluticasone propionate shows a protracted dissolution[28] and a slower rate of absorption (t_{max} after oral inhalation via Accuhaler®/Diskus® or pMDI is about 2 hours, mean absorption time is 6 to 8 hours).[29] This protracted dissolution may be advantageous, as drug retention at the target site is an important determinant of airway selectivity.[30] However, a reduced rate of dissolution will increase the amount available for mucociliary transport away from the airway target sites. In contrast, a high water solubility will increase the rate and extent of pulmonary uptake, which will increase intracellular accessibility and cytosolic receptor site concentrations. A high water solubility is also generally associated with a smaller volume of distribution and less peripheral tissue retention. This in turn should reduce the risk of accumulation and systemic effects. Hence, the pharmacological potency and airway selectivity of inhaled corticosteroids cannot be predicted from lipophilicity alone.

Relative intrinsic activity differs between different corticosteroids, and the most utilised inhaled corticosteroids (budesonide, beclomethasone dipropionate/beclomethasone monopropionate and fluticasone propionate) also have the highest intrinsic activities, as assessed by glucocorticoid receptor binding affinity (RBA) or vasoconstriction potency (fig. 1). However, although these assays show some correlation with clinical efficacy, this is not always the case. One example is tipredane, which has the highest RBA value of all topical corticosteroids tested for asthma, but a poor thera-

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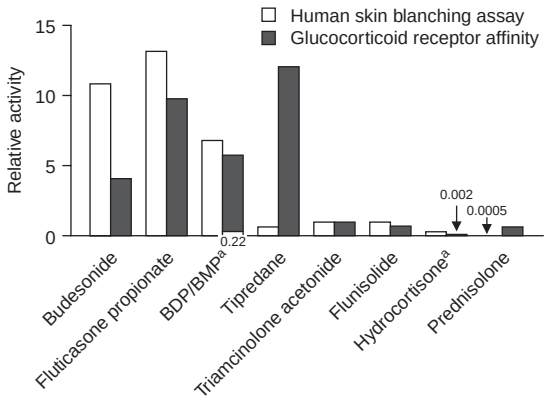

Fig. 1. Intrinsic activity of corticosteroids, assessed as affinity for the glucocorticoid receptor, or vasoconstriction using the McKenzie skin blanching test, relative to triamcinolone acetonide = 1. Skin blanching data were compiled from Brattsand and Axelsson,[31] Phillips,[32] Johansson et al.[33] and Lutsky et al.[34] Glucocorticoid receptor data were compiled from Brattsand and Axelsson[31] and Reed.[35] Glucocorticoid receptor affinity for BDP and BMP (0.22 and 5.7, respectively) is given for each compound separately. **a** indicates that a stripped skin version of the McKenzie vasoconstriction test was used; **BDP** = beclomethasone dipropionate; **BMP** = beclomethasone monopropionate.

peutic effect.[31] Other factors, both preceding and following the actual receptor interaction, may have as important or more important effects on the therapeutic outcome. Such factors include local metabolism, lung tissue concentrations and dwell time at the receptor site.

3. Airway Retention

Airway concentrations of corticosteroids have been relatively little studied. Peak tracheal concentrations of budesonide, fluticasone propionate and beclomethasone dipropionate were almost 100-fold greater than those after hydrocortisone and dexamethasone following a 10-minute tracheal superfusion to rats.[36] In humans, bronchoalveolar lavage : serum concentration ratios were assessed after intravenous injection of various water-soluble corticosteroids and ranged between 0.4 and 1.3 for methylprednisolone, prednisolone, dexamethasone and triamcinolone, with prednisolone being the highest and triamcinolone the lowest.[37] On the contrary, the drug concentration was found to be several-fold higher in lung than in plasma after inhalation of budesonide and fluticasone propionate.[38,39] These data thus suggest that after inhalation of the pharmacologically potent, locally acting corticosteroids, a considerably greater targeting is achieved compared with conventional treatment with systemic corticosteroids.

3.1 Fatty Acid Esterification of Budesonide

In spite of its relatively rapid rate of dissolution and moderate lipophilicity, budesonide appears to have a duration of action exceeding that of most of the currently available inhalation corticosteroids. The finding that budesonide was retained to a greater extent than the more lipophilic corticosteroids (fig. 2) was unexpected. Subsequent analyses of the tissue samples revealed that, whereas fluticasone propionate samples contained unchanged fluticasone propionate, budesonide samples, even at 20 minutes after administration, contained 80% or more of total radioactivity as budesonide oleate. Interestingly, later studies not only confirmed the formation of budesonide esters, but also showed that much lower amounts of esters are present in striated muscle, even after local injection of budesonide into an adjacent muscle: at 20 minutes after injection, only 12% of muscle radioactivity consisted of budesonide esters, while at the same time in the same experiment, there was a considerably greater portion in lung and trachea (approximately a 1 : 1 ratio of budesonide to budesonide ester).[40] These experiments indicate that budesonide is considerably more prone to form esters in trachea and lung than in muscle.

From biotransformation studies in human liver and lung microsomes and human bronchial cells *in vitro*,[41,42] several fatty acid esters of budesonide have subsequently been identified: the 21-palmitoleate, palmitate, linoleate, arachidonate and the quantitatively dominating oleate. Esters could be hydrolysed back to intact budesonide by

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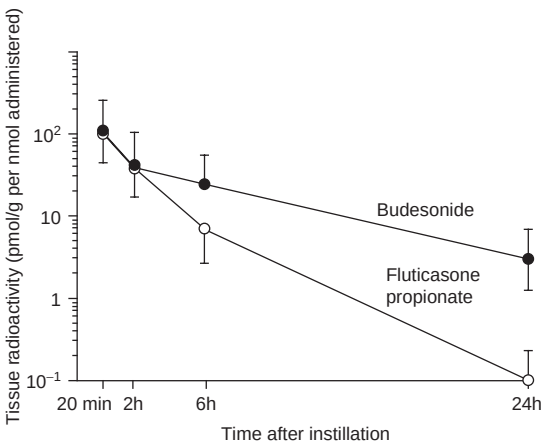

Fig. 2. Tracheal retention of radioactivity after intratracheal instillation of ^{3}H-labelled budesonide and fluticasone propionate in rats (n = 4 for each corticosteroid and time-point). Values are given as geometric means with 95% confidence intervals. (Data were taken from Miller-Larsson et al.,[36] with permission.)

lipases and cholesterol esterases. Fluticasone propionate, lacking the 21-hydroxy group, did not form corresponding fatty acid esters.[41] Unlike budesonide, the budesonide esters possess little affinity for the glucocorticoid receptor.[43] Lipopolysaccharide-evoked lung inflammation did not affect the propensity of airways to form budesonide esters.[44] Blocking of budesonide binding to the glucocorticoid receptor by the glucocorticoid antagonist mifepristone (RU-486) resulted in a relative increase of intracellular budesonide esters.[45] In contrast, the acyl-cholesterol CoA transferase inhibitor cyclandelate significantly reduced the intracellular content of esterified budesonide but not intact budesonide. The fatty acid esters are 500 to 10 000 times more lipophilic than budesonide itself. Reversible esterification with long chain fatty acids, similar to that observed with budesonide, serves as a storing process for cholesterol and some endogenous steroid hormones, including estrogens.[46]

Fatty acid esters of budesonide are formed also in human lung *in vivo*.[47] Central and peripheral lung tissue was obtained from 7 patients undergoing lung resection surgery. The concentrations of the total amount of budesonide fatty acid esters and budesonide were about the same. The ratio between budesonide and budesonide oleate was similar in central and peripheral lung samples.

Fatty acid esterification of budesonide probably prolongs anti-inflammatory action by increasing the dwell time within the airways. The anti-inflammatory effects of budesonide and fluticasone propionate were investigated in a corticosteroid-sensitive, transcription factor activation protein-1–mediated *in vitro* system, using transfected rat fibroblasts.[43] Experiments were performed either during continuous 24-hour incubation or during a 6-hour pulse exposure followed by extensive washing and a further 18-hour incubation with intact cells. The latter experiment was performed to mimic the clinically more relevant situation of intermittent airway exposure. Fluticasone propionate was significantly more potent than budesonide during continuous exposure over a wide concentration range. However, in the 6-hour pulse experiment, fluticasone propionate lost most of its effect, whereas most of that of budesonide remained. *In vivo*, a similar prolongation of anti-inflammatory effect was reported.[48]

4. Distribution and Elimination

All of the corticosteroids currently available for inhalation therapy appear to be inactivated by liver biotransformation, most commonly by oxidative metabolism via cytochrome P450 (CYP) 3A. Recent data suggest that the gut mucosa also contributes.[49] For most inhalation corticosteroids, hepatic elimination is efficient and systemic clearance is therefore close to liver blood flow. As a consequence, oral availability is low (table III). This will reduce the contribution of the swallowed fraction to overall systemic adverse effects. Fluticasone propionate and possibly mometasone furoate appear to have almost negligible oral availability,[51,52] whereas the other inhalation corticosteroids for which oral availability has been assessed have values in the range of 6 to 23% (table III). The recent improvement in delivery systems,

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Table III. Basic pharmacokinetic parameters of inhaled corticosteroids. (Reprinted from Barnes et al.,[50] with permission. ©American Lung Association 1998.) The pharmacokinetics of beclomethasone dipropionate/beclomethasone monopropionate have not yet been determined after intravenous or oral administration

Corticosteroid	Plasma half-life (h)	Volume of distribution (L/kg)	Clearance (L/min)	Oral availability (%)
Budesonide	2-3	2.7	0.9-1.3	6-13
Flunisolide	1.6	1.8	1.0	21
Fluticasone propionate	8-14	12.1	0.9-1.3	<2
Triamcinolone acetonide	1.5	1.3	0.7	23

with increased lung deposition and a reduced fraction being swallowed, has also reduced the negative impact of oral absorption.

The terminal plasma half-life of a drug may be determined by its rate of absorption, its rate of elimination, or, for a drug that is formed by metabolic activation, its rate of formation. For most of the inhaled corticosteroids, including the relatively slowly absorbed fluticasone propionate,[53] elimination appears to be rate limiting. The rate of elimination affects the amount of drug present in the body at steady state and by this the rate and extent of accumulation. Accumulation, in turn, is a function of the frequency of administration relative to the half-life of the drug, so that drugs having a terminal half-life of the same order of magnitude as the administration interval, or longer, will accumulate. A long elimination half-life will also reduce the peak : trough plasma concentration ratio. Persistent plasma concentrations of a corticosteroid may affect the hypothalamic-pituitary-adrenal (HPA) axis to a greater extent than high peak plasma concentrations.[54]

Lipophilicity correlates closely with volume of distribution.[27] Hence, fluticasone propionate is the most extensively distributed of the currently available corticosteroids, with a volume of distribution 2 to 4 times larger than most of the other inhaled corticosteroids (table III). This extensive distribution is the major cause for the relatively long plasma half-life found for this corticosteroid. There are currently no reliable pharmacokinetic data on beclomethasone dipropionate and its active monopropionate metabolite following intravenous or oral administration.

5. Clinical Implications

In a clinical context, airway selectivity is determined by the therapeutic effect in combination with the risk of causing clinically relevant adverse effects. This has been documented for most of the marketed inhaled corticosteroid formulations in placebo-controlled studies, but in few conclusive comparative studies versus other corticosteroids. Hence, most efficacy comparisons have been underpowered and/or undertaken at doses where effect is maximised, i.e. at the top of the dose-response curve.[50] As the doses needed to evoke measurable short term systemic effects are generally even higher, assessment of differences between corticosteroid formulations in airway selectivity under the same study protocol is extremely difficult. In a recent committee report from the Canadian Thoracic Society,[55] it was recommended that efficacy should be assessed in large double-blind parallel-group studies in mildly uncontrolled asthma with at least 3 doublings of the doses of each formulation or by using a stepwise corticosteroid-withdrawal design. Systemic effects should be assessed separately by 24-hour plasma cortisol assessments in healthy volunteers in placebo-controlled double-blind crossover studies.

Many of the pharmacokinetic prerequisites for airway selectivity appear to be fulfilled with the modern inhaled corticosteroid formulations. It still remains to be proven whether glucocorticoid receptor affinity, airway deposition and retention or other mechanisms, alone or in combination, are major determinants of therapeutic efficacy, and whether any one corticosteroid formulation is superior in this respect. Regarding the risk of systemic effects, probably a combination of low intrinsic potency, high clearance and low tissue

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retention is an important feature. Neither time of day nor single or divided daily doses appear to significantly affect the risk of systemic effects.[56] Fluticasone propionate is about 4 times more potent in affecting the HPA axis than budesonide or triamcinolone acetonide, as assessed in a recent meta-analysis.[57] This difference is most notable at the upper part of the clinically recommended dose interval, and is probably a result of the relatively marked tissue accumulation noted for fluticasone propionate.[51] In this context, the efficiency of the delivery system also needs to be taken into account.[58-60]

The clinical impact of fatty acid esterification on the airway selectivity of budesonide is currently being investigated. One clinical implication of the conjugation phenomenon may be the favourable profile of budesonide as a once-daily treatment regimen in mild to moderate asthma.[61,62] Human pharmacokinetic-pharmacodynamic modelling has also shown that the formation of budesonide esters is a mechanism by which not only the duration of action, but also the topical selectivity, of budesonide may be increased;[63] the high initial concentrations of budesonide in the lung lead not only to initial saturation of the glucocorticoid receptor but also to a prompt and large 'first-pass' budesonide ester pool in the airways. This increases the duration of action compared with a situation where budesonide esters are not formed. In addition, the rapid systemic dilution and the relatively moderate lipophilicity of unesterified budesonide will limit the nonspecific tissue retention of active drug as well as ester formation, in this way reducing the risk of systemic accumulation and systemic adverse effects.

One interesting approach to improving airway selectivity is to make the corticosteroid metabolically more 'soft' by extrahepatic metabolic inactivation, resulting in less systemic exposure. Metabolic stability in the target organ will be critical, and the therapeutic efficacy of such compounds still remains to be demonstrated.

6. Conclusion

For the inhaled corticosteroid formulations, many of the pharmacokinetic prerequisites for airway selectivity have been fulfilled, and most of the available corticosteroid formulations are highly efficacious while causing no systemic adverse effects in the majority of asthma patients. Still, there is room for improvements, and major challenges in the development of new improved corticosteroids include (i) increased retention at the target site while maintaining rapid systemic elimination, and (ii) increased extrahepatic inactivation. Budesonide, with its prompt esterification in airways but little peripheral retention, appears to partly fulfil the former feature; new 'soft' corticosteroids may provide the latter.

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