Pharmacokinetic and Pharmacodynamic Properties of Inhaled Ciclesonide

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Inhaled corticosteroids are recommended first-line therapy for persistent asthma of all severities; however, oropharyngeal and systemic adverse events can be a concern. Inhaled corticosteroids exert their therapeutic and adverse effects by interacting with glucocorticoid receptors within and outside the lungs, respectively. Ciclesonide is a novel inhaled corticosteroid that possesses a unique pharmacokinetic and pharmacodynamic profile. Ciclesonide is inactive itself and converted to its pharmacologically active metabolite, desisobutyryl-ciclesonide, in the target organ, the lungs. Pulmonary activation combined with low oral deposition may minimize oropharyngeal adverse events, and low oral bioavailability, rapid clearance, and high protein binding may reduce systemic exposure. In addition, high pulmonary deposition due to the highly respirable particles, combined with the potential for prolonged lung retention via lipid conjugation, provides for effective therapeutic action.

Keywords: *Ciclesonide; inhaled corticosteroids; safety; pharmacokinetic; pharmacodynamic*

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Asthma is a chronic inflammatory disorder of the airways, which results in variable, reversible airway obstruction, inflammation, and hyperresponsiveness.[1,2] The disease affects approximately 300 million people worldwide (20 million in the United States) and is associated with significant morbidity and mortality.[3,4] Treatments are available for management and control of the disease, which aim to allow patients to lead relatively normal lives, with minimal impact from symptoms or adverse events. Of these treatments, inhaled corticosteroids (ICS) are the most effective controller medications currently available and are recommended as first-line therapy for persistent asthma of all severities in national and international guidelines.[1,2] Inhaled corticosteroids have been shown to improve pulmonary function, relieve symptoms, and reduce exacerbations, airway hyperresponsiveness, and the need for acute reliever medication in patients with asthma.[1,5-8]

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A number of different ICS are currently available, including beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. All ICS exert their therapeutic effect by interacting with the same glucocorticoid receptors (GR) within the lungs, although with different binding affinities and potencies.[9-11] Receptor binding can be further influenced by the amount of time that the receptor is exposed to the drug as a result of differences in the delivered dose and its pulmonary deposition.[12] Similarly, the safety characteristics of these agents depend on multiple pharmacokinetic and pharmacodynamic (PK/PD) properties.[10]

Although the benefits of ICS therapy in patients with asthma far outweigh the potential for adverse events, ICS-related oropharyngeal (eg, oral candidiasis, dysphonia, and hoarseness) and systemic (eg, growth suppression, osteoporosis, disruption of hypothalamic–pituitary–adrenal [HPA]-axis function, skin thinning, and cataract formation) adverse events can be a concern for patients and clinicians.[13-17]

When considering the safety of ICS, there are several PK/PD properties that may influence systemic and oropharyngeal adverse events.[12,18-20] Ciclesonide is a novel ICS already approved in many countries and currently under development in the United

States for the treatment of asthma of all severities and possesses several PK/PD properties that may lead to a favorable safety profile. This article provides a comprehensive review of the currently known PK/PD properties of ciclesonide (Table I).

THE PATHWAY OF INHALED CORTICOSTEROIDS

When assessing the PK/PD properties of ICS, the fate of these agents first needs to be considered. Following inhalation, ICS are deposited either in the upper respiratory airways or directly into the lungs (Figure 1). Deposition and absorption of ICS into the lungs induces the desired therapeutic effect, after which it eventually enters the systemic circulation. However, although inhaler devices are designed to deliver drugs to the lungs, a large portion of the dose may be deposited in the oral cavity.[21] Orally deposited ICS may be swallowed and absorbed via the gastrointestinal (GI) tract and enter the systemic circulation.[21] For ICS that is absorbed from the GI tract, a portion will be metabolized by the liver before entering the systemic circulation. The total systemic ICS bioavailability, therefore, depends not only on the fraction of drug available to the lungs but also on the uptake and metabolism of the swallowed dose.[12,21,22]

PHARMACOKINETIC/PHARMACODYNAMIC PROPERTIES OF CICLESONIDE

In addition to the potency and affinity for the GR, the effectiveness of ICS therapy can be influenced by a number of factors such as oral and pulmonary deposition, lipophilicity, and lipid conjugation. Similarly, oropharyngeal and systemic safety are influenced by several characteristics, including oral deposition and bioavailability, plasma protein binding, and systemic clearance. In addition to these PK/PD properties, delivery devices also affect the oral and pulmonary deposition of ICS.

Pulmonary Deposition and Distribution

High pulmonary deposition increases the amount of ICS that reaches the lungs and thus, is able to elicit the desired therapeutic effect. Increased pulmonary deposition may also reduce the amount of drug that is deposited orally and, because more of the delivered dose reaches the lung, allow for the administration of lower doses of ICS. The distribution of ICS once it has reached the lungs is also important as asthma has been shown to be a disease of both the small and large airways.[23,24] In accordance with this, the size of delivered ICS particles can influence both pulmonary deposition and distribution. Because the internal perimeter of the smallest airways is ~2 μm, smaller particles generally infer higher pulmonary deposition and a more even distribution of ICS throughout the lungs.[22,25-27]

Various inhalation devices are available to deliver ICS to the lungs and numerous advances with these devices have been made to enhance lung deposition. Inhaled corticosteroids are generally delivered either via chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) metered-dose inhalers (MDI) or dry-powder inhalers (DPI); however, CFC-MDIs are currently being phased out in the wake of the Montreal Protocol on substances that deplete the ozone layer.[28] Irrespective of propellant, MDIs can be formulated as either solutions or suspensions. Solution-formulated HFA-MDIs have generally been shown to deliver a greater fraction of small particles than solution-formulated CFC-MDIs, suspension MDIs, or DPIs.[25,27,29] It should be noted, however, that the generation of fine particles is unique to each specific ICS and delivery device; as such, caution should be taken when generalizing the particle sizes of different agents administered via the same delivery device.

Ciclesonide has been formulated as a solution HFA-MDI with a majority of particles within the range of 1.1 to 2.1 μm.[30,31] This small particle size likely results in the high pulmonary deposition that has been demonstrated for ciclesonide.[31,32] Imaging studies have shown that 52% of the administered ciclesonide dose was deposited in the lung in both healthy subjects and in those with asthma.[31,32] Furthermore, ciclesonide that is deposited and converted into the active metabolite desisobutyryl-ciclesonide in the lungs showed a wide distribution, effectively penetrating the peripheral airways and thereby inducing therapeutic effect throughout the target organ.[32]

Receptor Binding and Pulmonary Activation

The therapeutic effects of the ICS are mediated via GR in the lungs. These receptors are widely distributed in the pulmonary system, with high expression levels in airway epithelial cells and bronchial vascular cells.[33] The potency of an ICS is assessed as the relative receptor affinity (RRA) versus dexamethasone, which is assigned a value of 100. Accordingly, for any given concentration, an ICS with a relatively high RRA will induce a greater anti-inflammatory effect than an ICS with a lower RRA. However, this

Table I Pharmacologic Properties of Ciclesonide and Desisobutyryl-Ciclesonide[30-32,34,43,51,52,61,65,75,76,82,83]

	Ciclesonide	Desisobutyryl-Ciclesonide
Formulation	Solution	—
Inhaled form	HFA-MDI	—
Particle size (MMAD) of respirable fraction	1.1–2.1 μm	—
Oropharyngeal deposition	5%-13%,* 33%-38%†	<20% of total oropharyngeal deposition of ciclesonide*
Oral bioavailability	<1%	<1%
Pulmonary deposition	52%	—
Lipid conjugation	—	Yes
Receptor binding affinity (relative to deamethasone)	12	1200
Protein binding	~99%	~99%
Volume of distribution‡	2.90 L/kg	12.06 L/kg§
Clearance‡	2.04 L/h/kg‖	3.04 L/h/kg§,‖
Elimination half-life‡	0.38 hours	3.5 hours

HFA-MDI, hydrofluoroalkane metered-dose inhaler; MMAD, mass median aerodynamic diameter.
* Values obtained from mouth-rinsing samples.
† Values obtained from 2D and 3D imaging.
‡ Values obtained from intravenous administration studies.
§ Assumes 100% conversion of ciclesonide to desisobutyryl-ciclesonide.
‖ Clearance via hepatic and extra-hepatic metabolic routes.

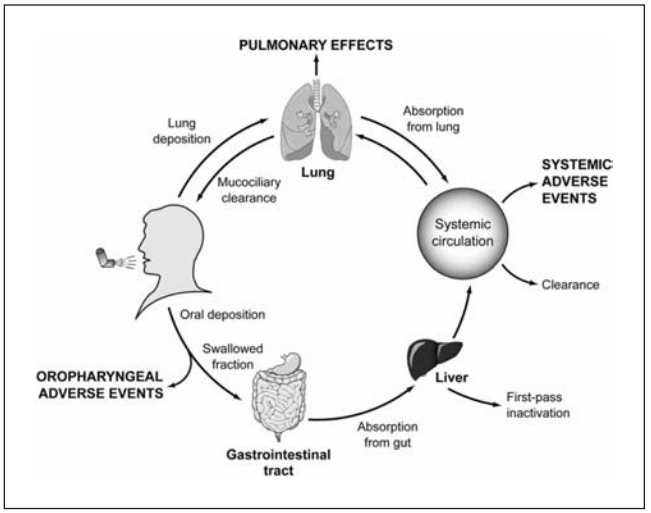

Figure 1. Pathway of inhaled corticosteroids.

effect can be moderated by increasing the concentration of an ICS with a low RRA.[12,22] As such, if present in equipotent concentrations at the GR, there is no appreciable difference in the efficacy of ICS. It is also worth noting that although a high receptor-binding affinity is desirable in an ICS with regard to therapeutic efficacy within the lungs, this may be offset by potent binding to GR outside the lungs, potentially resulting in adverse events. One approach for reducing the risk of ICS activity and associated adverse events in the throat and oral cavity is to deliver the agent as an inactive compound that is activated in the lungs to the therapeutically effective compound.

Ciclesonide uses such mechanisms as it is inactive itself (RRA = 12) and is hydrolyzed by carboxyesterases and cholinesterases to its highly potent active metabolite, desisobutyryl-ciclesonide (RRA = 1200), primarily in the airway epithelium of the upper and lower airways (Figure 2).[34-38] Specifically, bronchial epithelial cells activate ciclesonide to desisobutyryl-ciclesonide, which is then available to exert anti-inflammatory effect on the same bronchial epithelial cells, primarily via inhibition of interleukin-4 and tumor necrosis factor—α.[37] Recent in vitro data have also shown that ciclesonide significantly downregulates adhesion molecule expression in lung fibroblasts.[39] These findings suggest that in addition to activation in lung epithelial cells, lung fibroblasts also effectively convert ciclesonide into its active metabolite, desisobutyryl-ciclesonide, consequently exerting anti-inflammatory activity that may prevent airway remodeling.[39]

Collectively, the on-site activation of ciclesonide in the lungs, relatively high RRA of desisobutyryl-ciclesonide, and high pulmonary deposition are essential components that explain the anti-inflammatory action and efficacy observed in previous studies.[36,40,41]

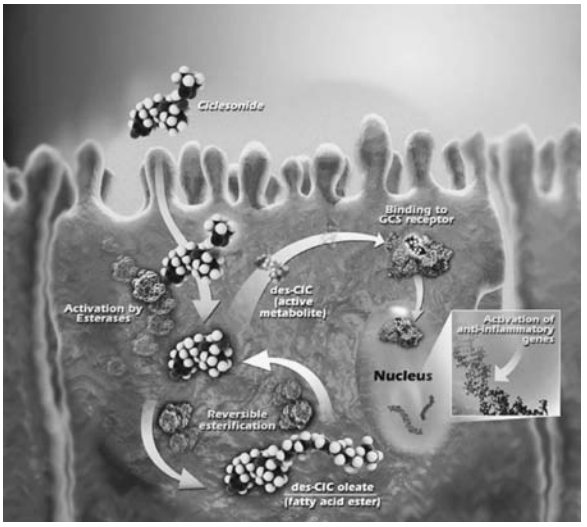

Figure 2. Intracellular activation of ciclesonide and reversible esterification of desisobutyryl-ciclesonide. des-CIC, desisobutyryl-ciclesonide; GCS, glucocorticosteroid. Reprinted from Nave et al,[43] copyright 2005, with permission from Elsevier.

Pulmonary Residence Time

The longer an ICS remains within the lungs, the longer it will elicit the desired therapeutic effects. In addition, although a longer retention time in the lungs will not reduce the overall systemic exposure to the drug, it may result in reductions in the maximal systemic exposure to the drug. Several methods have been employed for prolonging the residence time of ICS within the lungs, which include increasing drug lipophilicity and the formation of lipid conjugates.[35,42-47] Intracellular ICS conjugation to lipids prolongs pulmonary residence time by creating a reservoir of ICS that gradually becomes available over time to elicit an anti-inflammatory action. This prolonged pulmonary residence may also allow for once-daily dosing due to the extended therapeutic effect.[35,42-45] Studies with ciclesonide have demonstrated that following its conversion to the active metabolite in the lungs, desisobutyryl-ciclesonide forms reversible fatty acid conjugates (Figure 2).[35,43,48] The main fatty acid conjugate of desisobutyryl-ciclesonide has been shown to be desisobutyryl-ciclesonide oleate, which is highly lipophilic (logD 13.0).[35,49] Furthermore, in vitro studies showed that fatty acid conjugates of desisobutyryl-ciclesonide were present in the lung following 24 hours of incubation with [^{14}C]-ciclesonide,[35] and in vivo studies in rats have demonstrated that fatty acid conjugates of desisobutyryl-ciclesonide were present in the lungs ≥24 hours after inhalation of ciclesonide.[43] These data indicate that desisobutyryl-ciclesonide may be present within the lungs for a prolonged period, potentially due to the formation of highly lipophilic fatty acid esters.

Oropharyngeal Deposition and Pulmonary Activation

Oropharyngeal adverse events (oral candidiasis, dysphonia, pharyngitis) have been associated with both short- and long-term use of ICS[16,50] and may be related to deposition of drug in the upper airways. As such, reduced oropharyngeal deposition of ICS could reduce the potential for oropharyngeal adverse events. Additionally, on-site activation of ICS in the lungs would be expected to reduce deposition of pharmacologically active drug in the throat and, therefore, further reduce the potential for oropharyngeal adverse events.

Ciclesonide has demonstrated relatively low oropharyngeal deposition (~30%).[32] This may be due to the HFA-MDI device used for delivery and small particle size (1.1–2.1 μm).[30] In addition, because the active drug is generated on-site in the lungs, the presence of pharmacologically active drug (desisobutyryl-ciclesonide) in the throat is minimal.[51,52] Indeed, studies have shown that <20% of the residual ciclesonide present in the oropharynx was metabolized to desisobutyryl-ciclesonide.[51,52] The low oropharyngeal deposition of ciclesonide, combined with its minimal activation in the oropharynx, may explain the low rate of oropharyngeal adverse events that have been observed with this agent in clinical studies.[53-59]

Oral Bioavailability

The systemic bioavailability of an ICS equals the sum of the fraction deposited in the lungs as well as the unmetabolized fraction that is swallowed. Any swallowed drug may be absorbed into the system via the GI tract. This fraction may then be metabolized in the liver (first-pass metabolism) or enter the systemic circulation still active. Although the fraction of ICS that enters the systemic circulation via this route is potentially much less than that entering through the lungs, GI-absorbed ICS will not elicit any therapeutic effect on route and thus only contributes to total systemic exposure and potential adverse events. Ideally, oral bioavailability should

be limited to reduce the systemic availability of ICS therapies and potential for adverse events.[21]

As described above, ciclesonide has a low oral deposition, which, combined with its rapid metabolism in the liver by cytochrome P450 3A4 isozymes,[60] may explain the low oral bioavailability that has been observed for both ciclesonide and desisobutyryl-ciclesonide (<1%).[61] Furthermore, when ciclesonide was coadministered with erythromycin (a cytochrome P450 3A4 inhibitor) in 18 healthy volunteers, no change in the PK properties of either compound was demonstrated, indicating that ciclesonide metabolism is unlikely to be affected by drug–drug interactions.[62] For ciclesonide, therefore, the majority of the systemic exposure will be a result of uptake through the lung.

Plasma Protein Binding

Freely circulating protein-unbound ICS in the systemic circulation is able to interact with GR outside the lungs and, potentially, induce systemic adverse events.[63] Plasma protein binding of ICS (eg, to albumin, α_1-acid glycoprotein) can reduce the potential for systemic adverse events by reducing the number of freely circulating, pharmacologically active molecules that are able to interact with receptors outside the lungs.[22,64,65] Indeed, protein binding rates have been demonstrated to provide valuable markers in predicting the cortisol suppression of ICS.[66]

Ciclesonide and desisobutyryl-ciclesonide have both demonstrated protein binding rates of ~99% with no apparent saturation of protein binding observed at high doses.[65,67] In a recent study, administration of supra-therapeutic doses of ciclesonide (2880 μg) to healthy volunteers resulted in a total maximum serum concentration of desisobutyryl-ciclesonide (both bound and unbound) of 2930 ng/L.[68,69] Further analysis of microdialysis samples demonstrated the low interstitial concentrations of unbound desisobutyryl-ciclesonide, which were below the lower limit of quantitation (<0.025 μg/L) in both skeletal muscle tissue and subcutaneous adipose tissue.[68,69]

The high plasma protein binding of ciclesonide may help explain the minimal effect on HPA-axis function and cortisol levels (surrogate markers for ICS bioavailability) observed with this agent at doses of up to 1280 μg/d.[6,59,70-74]

Clearance and Half-Life

As previously discussed, systemic adverse events can be induced by freely circulating, pharmacologically active ICS. Efficient elimination (clearance) from the systemic circulation is crucial for ICS and reduces the period in which molecules are able to interact with GR outside the lungs.

For drugs that are only metabolized in the liver, the highest clearance possible corresponds to that of the liver blood flow of ~90 L/h. Desisobutyryl-ciclesonide is reported to have an apparent clearance rate of 228 L/h[75] (established via intravenous administration of ciclesonide; assumes an average weight of 75 kg), suggesting that there may be additional extra-hepatic metabolism routes in operation. The mean elimination half-life has been reported as ~3.5 hours.[61,76] Based on the assumption of complete conversion of ciclesonide to desisobutyryl-ciclesonide, these findings indicate that this compound will be rapidly cleared from the system.

DISCUSSION

The PK/PD properties of ICS directly affect their efficacy and safety profiles, and understanding these PK/PD properties has allowed the development of new compounds. Inhaled corticosteroids should provide effective asthma control with a minimal potential for oropharyngeal adverse events and negligible systemic activity. For safety, an ICS should possess high pulmonary deposition, pulmonary activation for targeted delivery, negligible oral deposition and bioavailability, high plasma protein binding, and rapid systemic clearance. In terms of efficacy, high pulmonary deposition with pulmonary activation for targeted delivery, high receptor binding, and prolonged pulmonary effect via lipid conjugation would all be desirable attributes in an ICS. In addition to the inherent chemical properties of an ICS, the delivery device and formulation are also important and will affect the proportion and distribution of the drug that is delivered to the lungs.

Ciclesonide is inactive itself and is converted to its active metabolite, desisobutyryl-ciclesonide, in the lungs, which, combined with its low oral deposition, may minimize oropharyngeal adverse events, as has been observed in clinical trials.[53-59] In addition, low oral bioavailability, rapid metabolism, and high protein binding reduce systemic exposure and, therefore, adverse events, which may explain the lack of effect ciclesonide has demonstrated on HPA-axis function and cortisol levels.[6,59,70-74] Furthermore, high pulmonary deposition and distribution in the lungs due to the highly respirable particles, combined with the potential for prolonged lung retention via lipid

conjugation, provide a rationale for the observed efficacy in a number of clinical trials.[8,57,77-81]

CONCLUSION

The PK/PD characteristics of ciclesonide offer a rationale that supports the safety and efficacy observed in clinical trials. These properties suggest that ciclesonide may have a favorable risk–benefit profile for the treatment of persistent asthma.

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