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AN OVERVIEW OF PHARMACODYNAMIC PROPERTIES OF INHALED CORTICOSTEROIDS

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Abstract:

This article was aimed to review the pharmacodynamic of inhaled corticosteroids, by conducting search throughout the literature, using the PubMed and Medline, including all relevant studies that were published to beginning of 2022. The PK and PD properties of ICSs used to treat asthma, as well as the significance of their interactions, have been studied. When prescribing an ICS to an asthmatic patient, the differences in PK and PD must be considered because a better understanding of the PK/PD interrelationship of ICSs may be important to better fit with the between-patient variability and within-patient repeatability in the response to ICSs, which frequently complicate the therapeutic approach to the asthmatic patient.

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INTRODUCTION:

Asthma is a chronic inflammatory airway illness that causes fluctuating, reversible airway obstruction, inflammation, and hyperresponsiveness [1]. The disease affects roughly 300 million individuals globally and has a high morbidity and mortality rate [2,3]. Treatments for disease management and control are available, with the goal of allowing patients to live relatively normal lives with minimum impact from symptoms or adverse events. Inhaled corticosteroids (ICS) are the most effective controller medicines now available and are recommended as first-line therapy for all severities of persistent asthma in national and international recommendations [2].

Inhaled corticosteroids (ICSs) remain the first-line anti-inflammatory therapy for all severities of chronic asthma [4]. They impact hyperresponsiveness by reducing airway inflammation. ICSs increase lung function and symptom severity in this way [4]. They are also useful in preventing or reducing the frequency of asthma exacerbations [4]. The ability of ICSs to target all of the cells involved in asthmatic inflammation is linked to their anti-inflammatory activity [5]. ICSs decrease the expression and release of a wide range of inflammatory mediators and growth factors from primary airway epithelial cells, most likely by targeting nuclear factor-B (NF-B) or activator protein-1 (AP-1) and altering histone acetylation/deacetylation [5]. The anti-inflammatory activity of ICSs is elicited at the site of action in the airways. However, when ICS concentrations in the airways surpass certain thresholds, they are not in equilibrium with downstream systemic medication concentrations, which dictate the occurrence of severe systemic effects [6]. This finding emphasizes the importance of understanding the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the ICS to be used, as it is possible that it is very potent in terms of PD but has a poor PK profile, or vice versa, and the PK profile can affect its efficacy and/or therapeutic ratio. The study of the time course of drug absorption, distribution, metabolism, and excretion is referred to as PK, whereas PD refers to the relationship between drug concentration at the site of action and the resulting effect, which includes the time course and intensity of therapeutic and adverse effects. Several ICSs have been licensed for use in the treatment of asthma. Beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetate are among them. Variances in PK features of ICSs have a substantial impact on their profile [6], but significant differences in glucocorticoid receptor (GR) selectivity, potency, and physicochemical properties are also important in establishing an ICS's PD profile [6]. Beclomethasone dipropionate and ciclesonide are prodrugs that are converted to active metabolites by esterases present in the lungs and other organs. Beclomethasone-17-monopropionate is a substantially more potent conversion product of beclomethasone dipropionate. Conversion occurs in the lung (97%) [6]. Desisobutyrylciclesonide, a ciclesonide derivative, is also significantly more effective than its prodrug, with a 100-fold larger relative GR binding affinity [7]. Endogenous esterases in the airways enable ester cleavage conversion.

DISCUSSION:

There are currently several ICS on the market, including beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. All ICS work therapeutically by interacting with the same GR within the lungs, but with varying binding affinities and potencies [8,9]. The amount of time that the receptor is exposed to the medication as a result of changes in the administered dose and its pulmonary deposition can also alter receptor binding. Similarly, the safety of these agents is determined by a variety of pharmacokinetic and pharmacodynamic (PK/PD) aspects. Although the benefits of ICS therapy far outweigh the risks of adverse events in patients with asthma, ICS-related oropharyngeal (e.g., oral candidiasis, dysphonia, and hoarseness) and systemic (e.g., growth suppression, osteoporosis, disruption of hypothalamic-pituitary-adrenal [HPA]-axis function, skin thinning, and cataract formation) adverse events can be concerning There are numerous PK/PD features that may influence systemic and oropharyngeal adverse events when examining the safety of ICS [8,9,10].

After passing through the phospholipid double layer of pulmonary cell membranes and being coupled to the GRs extensively expressed in most cell types throughout the body, ICSs initiate their clinical anti-inflammatory response [5]. The binding of GRs results in transcriptional regulation of target genes. The type I or mineralocorticoid receptor (nuclear receptor subfamily 3, group C, member 2; NR3C2) and the type II or glucocorticosteroid receptor (nuclear receptor subfamily 3, group C, member 1; NR3C1; GR) are the two types of GRs [11,12]. The currently available ICSs can connect to the second class of receptors in a unique way [13]. Inserting a 1,2 double bond and halogen atoms in the position on carbon atoms 6 and 9 reduces binding to the type I receptor and improves potency and stability against metabolism, whereas

lipophilic substituents such as 16- and 17-acetals, 17-esters, and 21-esters attached to the D-ring increase GR binding affinity [13,14]. The ligand-binding domain of GR has a pocket on the floor of the binding cleft [5]. GR, the traditional receptor that mediates the majority of known glucocorticoid activities, and GR, which come from the same gene by alternate splicing of the GR main transcript, have been identified as human isoforms of type II GR. Within the cell, GR is trapped in the cytoplasm by a massive multiprotein complex that contains chaperone proteins (hsp90, hsp70, and p23) and immunophilins (FK506-binding protein [FKBP]51 and FKBP52), preventing it from migrating to the nucleus. When a corticosteroid binds to a receptor, the ligand-glucocorticoid complex hyperphosphorylates, dissociates from the multiprotein complex, and migrates to the nucleus, where it binds as a homodimer to the DNA sequences, called GR response elements (**Fig. 1**) [9]. The resultant complex serves as an activator or repressor of proteins that activate RNA polymerase II transcription of some genes. The majority of the ICS-induced systemic deleterious effects appear to be connected with transcription machinery-induced transactivation activities and protein synthesis [9]. The interaction between the ligand-glucocorticoid complex and other transcription factors, such as NF-B or AP-1, which generally elicit the synthesis of proinflammatory cytokines, induces transrepression by causing their inactivation, which leads to decreased production of proinflammatory cytokines and, consequently, anti-inflammatory activity [6]. Even at modest ICS concentrations, this last action happens. Activated GRs engage with co-repressor molecules to reduce NF-B-associated coactivator activity, resulting in decreased histone acetylation, chromatin remodelling, and RNA polymerase II activity [13]. In fact, GRs attract histone deacetylase 2 (HDAC2), which suppresses the activated inflammatory genes [13]. GR does not bind ligand, is mostly found in the nucleus, and has no effect on glucocorticoid-responsive reporter genes [14]. In the presence of GR, however, GR functions as a dominant negative inhibitor, antagonizing GR activity on several glucocorticoid-responsive target genes. Even at modest ICS concentrations, this last action happens. Activated GRs engage with co-repressor molecules to reduce NF-B-associated coactivator activity, resulting in decreased histone acetylation, chromatin remodelling, and RNA polymerase II activity [13]. In fact, GRs attract histone deacetylase 2 (HDAC2), which suppresses the activated inflammatory genes [13]. GR does not bind ligand, is mostly found in the nucleus, and has no effect on glucocorticoid-responsive reporter genes [14]. In the presence of GR, however, GR functions as a dominant negative inhibitor, antagonizing GR activity on several glucocorticoid-responsive target genes. An ICS's action is influenced by affinity and effectiveness [9]. They are two PD criteria that are interrelated. Affinity describes the strength with which an ICS binds to a GR and is constant across tissues within a species [9]. The extent to which the pocket on the bottom of the binding cleft is occupied determines the affinity, as well as the length of action and safety profile of any one ICS [6]. Efficacy, which, as previously stated, measures an ICS's ability to produce a pharmacological effect and is influenced by tissue-dependent factors such as the response of interest (lung function, airway hyperresponsiveness, asthma symptom control, exacerbations, sputum, and exhaled markers of inflammation), receptor density, and receptor-effector coupling effectiveness [9].

The PK of ICSs Although the "new generation" of inhaler devices has a pulmonary deposition fraction of 40-60% of the nominal dose, which is significantly higher than the 10-15% of older devices [13], a significant portion of the dose of any ICS deposits directly in the oropharynx, central airways, or alveoli, depending on particle size and delivery device [17]. Particles greater than 5 m in size likely to settle in the mouth-throat area. If the oropharyngeal dose is not thoroughly rinsed from the mouth, the majority of it is swallowed and absorbed through the gastrointestinal tract. The portion of the dosage that does not get inactivated by first-pass metabolism in the gut or liver becomes systemically accessible [18]. The majority of the dose that enters the lung is absorbed into the systemic circulation via the bronchial and pulmonary arteries (pulmonary bioavailability). One-quarter of cardiac output is first-passed to the liver, resulting in corticosteroid inactivation, whereas the majority of airway/lung absorbed corticosteroid is broadly dispersed before finally undergoing hepatic metabolism [19]. As a result, an ICS's blood concentration is determined by the sum of its pulmonary and orally absorbed fractions that survive hepatic first-pass inactivation [20]. The amount of ICS that is systemically accessible is affected by the efficiency of first-pass hepatic metabolism. Fluticasone furoate, fluticasone propionate, mometasone furoate, and ciclesonide have high first-pass metabolism, whereas budesonide, flunisolide, triamcinolone acetonide, and beclomethasone dipropionate have low [13]. Fluticasone furoate, fluticasone propionate, mometasone furoate, and ciclesonide have 1% oral bioavailability in healthy persons, budesonide has 11%, flunisolide has 20%, triamcinolone acetonide has 23%, and

beclomethasone dipropionate has 41% [3]. Systemic drug concentrations influence systemic effects, whereas the amount of ICS entering the lungs induces the desired pharmacological action [20]. As previously stated, while employing the "new generation" of inhaler devices, roughly 40%-50% of the ICS dose is deposited in the lungs [13]. Characterization of its distribution into the lungs requires a dynamic interaction of several factors, including the type of delivery device used and its effectiveness, the drug formulation (solid or liquid), the site of ICS deposition, and clearance mechanisms such as mucociliary clearance and endocytosis [21]. It is also impacted by patient characteristics such as inhalation mode, effort, technique, and peak inspiratory flow rate [30]. In any case, not all ICSs are administered in their bioactive form. As previously stated, inhaled inactive molecules, ciclesonide and beclomethasone dipropionate, are transformed into active metabolites, desisobutyryl-ciclesonide and beclomethasone-17-monopropionate, by the activity of esterases found in the lung epithelium but not in the oropharynx [18,21].

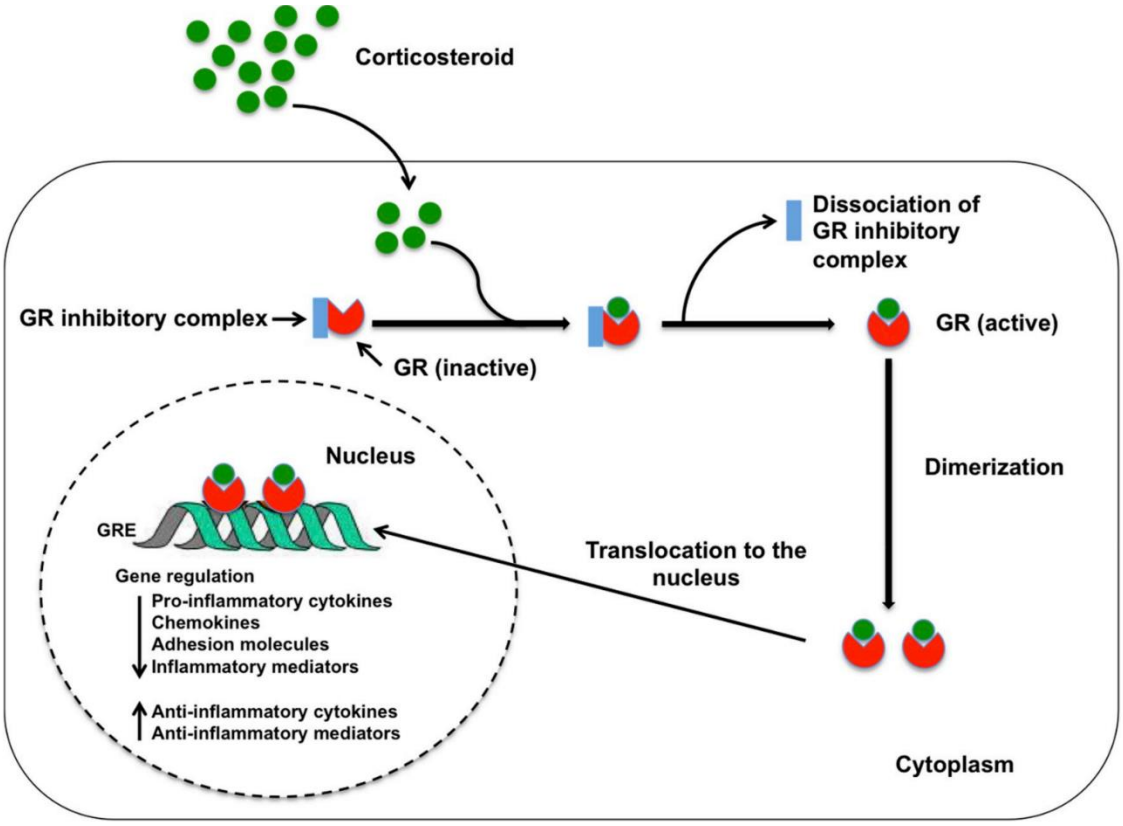

Fig. 1. Mechanism of corticosteroid signaling

Pulmonary Residence:

Time The longer an ICS stays in the lungs, the longer it will exert its therapeutic benefits. Furthermore, while a longer retention time in the lungs will not lower overall systemic exposure to the drug, it may reduce peak systemic exposure to the drug. Several approaches have been used to extend the residence period of ICS in the lungs, including enhancing drug lipophilicity and the production of lipid conjugates [22,23]. Intracellular ICS conjugation to lipids increases pulmonary residence time by forming a reservoir of ICS that gradually becomes accessible over time to trigger an anti-inflammatory effect. Because of the prolonged therapeutic effect, this prolonged pulmonary residency may also allow for once-daily dosage. Desisobutyryl-ciclesonide generates reversible fatty acid conjugates after being converted to the active metabolite in the lungs, according to studies with ciclesonide [24].

Oropharyngeal Deposition and Pulmonary Activation:

Oropharyngeal side effects (oral candidiasis, dysphonia, pharyngitis) have been linked to both short- and long-term ICS use and may be connected to drug deposition in the upper airways. As a result, decreased oropharyngeal ICS deposition may minimize the risk of oropharyngeal adverse events.

Furthermore, on-site activation of ICS in the lungs is expected to minimize pharmacologically active drug deposition in the throat, lowering the risk of oropharyngeal side effects. Ciclesonide has been shown to have a low oropharyngeal deposition (30%) [25,26]. This could be attributed to the HFA-MDI device employed for administration as well as the small particle size (1.1-2.1 m). In addition, because the active drug is generated on-site in the lungs, the presence of pharmacologically active drug (desisobutyrylciclesonide) in the throat is minimal [27].

CONCLUSION:

The PK properties of ICSs, particularly their interplay, may have an impact on their effectiveness and safety profiles. When prescribing an ICS to an asthmatic patient, the differences in PK and PD amongst ICSs must constantly be noted. Indeed, a greater knowledge of the PK/PD interplay of ICSs may be necessary to better align with the between-patient variability and within-patient repeatability in response to ICSs, which frequently complicates the therapeutic approach to the asthmatic patient. The pharmacokinetic characteristics of inhaled corticosteroids currently utilized in medical practice varied significantly. All are promptly eliminated from the body, although they differ in terms of oral bioavailability and, more critically, the rate of absorption following inhalation. Fluticasone propionate has the lowest oral bioavailability, indicating a reduced risk of undesirable systemic corticosteroid effects.

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