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EXPLORATORY STUDY ON THE ROLE OF INHALED CORTICOSTEROIDS IN ASTHMA MANAGEMENT

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Abstract:

Asthma is a chronic, heterogeneous respiratory disorder characterized by persistent airway inflammation, hyperresponsiveness, and structural remodeling, resulting in recurrent episodes of wheezing, dyspnea, chest tightness, and coughing. The etiology of asthma involves complex interactions between genetic predisposition, environmental exposures, and immune dysregulation. Accurate diagnosis requires comprehensive clinical evaluation supported by lung function tests and assessment of airway inflammation. Asthma management prioritizes inhaled corticosteroids (ICS) as the cornerstone therapy due to their potent anti-inflammatory effects mediated through glucocorticoid receptor binding and modulation of pro-inflammatory cytokines and immune cells. Common ICS agents—beclomethasone dipropionate, budesonide, and fluticasone propionate—exhibit distinct pharmacological profiles that guide individualized treatment. Effective ICS use improves airway function, reduces exacerbations, and enhances patient quality of life. Optimal outcomes depend on proper inhaler technique, dose titration, and mitigation of local and systemic side effects. Adjunctive therapies including beta-2 agonists, leukotriene receptor antagonists, and biologics complement ICS, particularly in severe or steroid-resistant cases. Comprehensive asthma care also encompasses trigger avoidance, patient education, and regular monitoring. This review underscores the critical role of ICS in asthma management and highlights the importance of personalized, multidisciplinary approaches to achieve sustained disease control and improved long-term respiratory health.

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INTRODUCTION:

Asthma is a chronic respiratory condition characterized by persistent inflammation of the airways. The disease involves multiple immune and structural cell types, including mast cells, eosinophils, T cells, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation results in recurrent episodes of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and coughing, which frequently occur at night or in the early morning hours.1

These exacerbations are typically associated with diffuse, yet variable, airway narrowing that often resolves spontaneously or in response to therapeutic intervention. The underlying inflammatory process also heightens airway hyperresponsiveness to various stimuli. While a majority of patients experience complete reversibility of airflow obstruction, a subset may exhibit only partial reversibility .This clinical definition, analogous to that of chronic sinusitis, emphasizes the presence of inflammation and related symptoms without delineating the precise etiology, which remains incompletely understood, nor the natural history of the disease, which may demonstrate considerable heterogeneity.2

Etiology:

Asthma is a multifactorial disease with an etiology that remains incompletely understood, involving complex interactions between genetic and environmental factors. Genetic predisposition is significant, with heritability estimates ranging from 35% to 95%, and numerous genetic variants have been linked to increased asthma susceptibility. Epigenetic modifications also contribute to disease development. Early-life respiratory viral infections notably elevate asthma risk , while exposure to airborne pollutants, tobacco smoke, and inhalant allergens further exacerbates susceptibility3.

Tissue remodeling in asthma involves structural alterations predominantly in the airway mucosa and submucosa, including epithelial hyperplasia, increased goblet cell numbers with mucus hypersecretion, smooth muscle hypertrophy, collagen deposition, and glandular enlargement. These changes contribute to airway narrowing and hypersecretion, underpinning the clinical manifestations of airway obstruction in asthma.4

Symptoms of Asthma:

Asthma exacerbations result from airway narrowing driven by inflammation and edema, excessive mucus secretion, and bronchial smooth muscle constriction .These episodes manifest as airflow obstruction, leading to symptoms such as dyspnea, wheezing, chest tightness, and cough.5

Common triggers encompass respiratory viral infections (notably rhinovirus), tobacco smoke, airborne allergens (dust mites, pet dander, pollen, mold, cockroach allergens), air pollution (PM2.5, PM10, ozone), abrupt temperature changes, emotional and psychological stress, and certain medications such as NSAIDs. These factors provoke airway inflammation and hyperresponsiveness, precipitating asthma episodes.6

Types of Asthma:

Asthma is a heterogeneous condition comprising multiple subtypes distinguished by distinct genotypes, phenotypes, and endotypes, reflecting variations in clinical presentation and underlying biological mechanisms (References 24, 25). Classification remains complex, with emphasis shifting toward endotypes that define asthma by specific pathophysiological pathways, driven by genetic and epigenetic factors. This stratification facilitates targeted therapeutic approaches, particularly with biologics aimed at inflammatory mediators such as IL-4 and IL-5.7,8

Common asthma subtypes include:

1. Cough-variant asthma:characterized by isolated chronic cough without classic bronchospasm symptoms.
2. Exercise-induced asthma:symptom onset or exacerbation triggered by physical exertion.
3. Allergic asthma:triggered by exposure to environmental allergens and often comorbid with atopic conditions.
4. Eosinophilic asthma:marked by elevated eosinophil levels and type 2 inflammation, responsive to biologic therapy.
5. Pediatric and adult-onset asthma:differing in etiology, triggers, and clinical course.
6. Steroid-resistant asthma:exhibiting poor response to corticosteroids, necessitating alternative treatments.9

Diagnosis of Asthma:

Asthma diagnosis involves a comprehensive clinical evaluation, including detailed patient history, physical examination, and lung function testing with spirometry or whole-body plethysmography to detect airflow obstruction and assess reversibility with bronchodilators .10 In absence of obstruction, bronchial hyperresponsiveness testing may be utilized. Routine allergy assessment through history, skin prick testing, and serum-specific IgE measurement is recommended. Measurement of fractional exhaled nitric oxide (FeNO) serves as an adjunct to evaluate airway inflammation.11

In severe asthma, differential diagnosis is critical to exclude mimicking conditions, including COPD, particularly in smokers. This entails acute and subacute reversibility testing with bronchodilators and systemic corticosteroids, respectively (Reference 10). Chest computed tomography (CT) is advised to identify structural abnormalities or alternative pathologies when clinical presentation is atypical. Additional diagnostics such as bronchoscopy for airway examination and biopsy, echocardiography for cardiac assessment, and 24-hour pH monitoring for gastroesophageal reflux disease may be indicated to inform comprehensive management.13,14

Treatment of Asthma:

1. Beta-2 Adrenergic Agonists
   Short-acting agents such as albuterol provide rapid bronchodilation within 15–30 minutes, lasting approximately 3–4 hours. These are available via metered-dose inhalers and nebulizers, with nebulization reserved for patients unable to use inhalers. The R-isomer is pharmacologically active; levalbuterol, a purified R-isomer, offers uncertain clinical advantage. Oral formulations exist but are less favored due to increased side effects. Terbutaline is uniquely available for subcutaneous administration in severe exacerbations.15
2. Muscarinic Antagonists
   These agents inhibit acetylcholine at muscarinic receptors, mitigating vagally mediated bronchoconstriction and mucus secretion. Their efficacy varies with stimulus and individual response, given their selective receptor activity.16
3. Inhaled Corticosteroids (ICS)
   ICS remain the cornerstone of anti-inflammatory asthma management, reducing airway hyperreactivity and inflammatory cell infiltration through cytokine suppression. While not direct bronchodilators, they improve airflow by attenuating mucosal edema and potentiating β-agonist effects.17
4. Leukotriene Receptor Antagonists (LTRA)
   Targeting leukotriene pathways, agents such as montelukast inhibit bronchoconstriction and airway inflammation. Although less efficacious than ICS in pulmonary function improvement, their oral administration is advantageous, particularly in pediatric populations.18
5. Methylxanthines
   Theophylline exerts bronchodilatory and anti-inflammatory effects via phosphodiesterase inhibition and adenosine receptor antagonism. Owing to a narrow therapeutic window and notable toxicity risk, therapeutic monitoring is imperative.19
6. Mast Cell Stabilizers
   Cromolyn and nedocromil, formerly prevalent as prophylactic treatments, now see limited use. Administered via inhalation, they prevent allergen- or exercise-induced asthma by reducing airway sensitivity but lack efficacy in acute symptom relief.20
7. Monoclonal Antibodies (Biologics)
   Omalizumab, an anti-IgE monoclonal antibody, attenuates allergic asthma by preventing IgE binding to effector cells, thereby reducing exacerbation frequency and corticosteroid dependency. Reserved for moderate to severe cases refractory to conventional therapy, it represents a high-cost but efficacious option.21

Overview of Inhaled Corticosteroids in Asthma Management:

Inhaled corticosteroids (ICS) are the cornerstone of asthma therapy, exerting potent anti-inflammatory effects primarily through modulation of gene transcription. They suppress the expression of multiple pro-inflammatory cytokines implicated in asthma pathogenesis, including IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, and GM-CSF, by binding to glucocorticoid response elements (nGREs) and repressing transcriptional activity Notably, cytokines such as IL-6 display heightened sensitivity due to multiple nGRE sites within their promoter regions. ICS further enhance cytokine mRNA degradation and downregulate cytokine receptor expression, exemplified by inhibition of IL-2 receptor synthesis.22

Glucocorticoid receptors (GR) counteract pro-inflammatory transcription factors including AP-1 and NF-κB, thereby attenuating T-cell activation and cytokine production. Additionally, ICS inhibit inducible nitric oxide synthase, reducing nitric oxide-mediated airway edema, and suppress genes encoding inflammatory mediators such as the NK1 receptor and endothelin-1, while upregulating protective enzymes like neutral endopeptidase that degrade inflammatory neuropeptides.23

Histopathological studies corroborate these mechanisms, demonstrating significant reductions in eosinophils, macrophages, mast cells, and lymphocytes following ICS treatment, effects not observed with β2-agonist monotherapy.24 CS also decrease eosinophil cationic protein levels, indicative of reduced eosinophil activation, and facilitate repair of the airway epithelium by restoring the balance between ciliated and mucus-producing goblet cells.

Although ICS may modestly reduce subepithelial basement membrane thickening a hallmark of airway remodeling this change is often incomplete even after prolonged therapy.25

Commonly utilized ICS in asthma include beclomethasone dipropionate, budesonide, and fluticasone propionate, all of which contribute significantly to controlling airway inflammation and improving clinical outcomes.26

Beclomethasone Dipropionate: Pharmacological Overview and Mechanism of Action:
Beclomethasone 17,21-dipropionate (BDP) is a corticosteroid agent extensively utilized in the topical management of asthma and allergic rhinitis. Initially introduced in 1972 as a pressurized metered-dose inhaler (MDI), BDP has since been developed into various formulations including dry powder inhalers and nasal sprays, thereby broadening its clinical applicability.27

BDP functions as a prodrug exhibiting minimal intrinsic glucocorticoid activity upon administration. It undergoes enzymatic hydrolysis by esterases to generate its active metabolite, beclomethasone 17-monopropionate (17-BMP), which exhibits high affinity binding to glucocorticoid receptors localized within cells of the respiratory tract.
Upon inhalation or intranasal administration, BDP is absorbed via the pulmonary or nasal mucosa, with an additional fraction being swallowed and absorbed gastrointestinally. The relative contribution of systemic exposure from pulmonary/nasal absorption versus gastrointestinal absorption remains incompletely defined.28

Mechanism of Action:
Following administration, BDP is rapidly converted to 17-BMP, which binds intracellular glucocorticoid receptors. The resulting receptor-ligand complex translocates to the cell nucleus, where it modulates gene transcription. This genomic regulation leads to the suppression of inflammatory cell activity, including eosinophils, T-lymphocytes, and mast cells, and diminishes the synthesis of inflammatory mediators such as cytokines and chemokines. Consequently, this cascade results in reduced inflammation, edema, mucosal irritation, and mucus hypersecretion, thereby ameliorating clinical symptoms.29

Pharmacological Pathway:
- Administration of BDP
- Metabolism by esterases
- Conversion to active metabolite 17-BMP
- Binding of 17-BMP to glucocorticoid receptors
- Formation of receptor-ligand complex
- Nuclear translocation of complex
- Regulation of gene expression
- Anti-inflammatory effects via reduction of inflammatory cell activity and mediator production
- Clinical outcome: decreased inflammation, swelling, irritation, and mucus production

Drug Interactions:
BDP may interact with various pharmaceuticals, warranting caution:
- Contraindicated with desmopressin and mifepristone.
- Generally avoided but sometimes necessary with agents such as aspirin, carbamazepine, insulin aspart, and phenytoin.
- May potentiate side effects when combined with auranofin or live rotavirus vaccine, though sometimes clinically required

Dosage and Duration:
Dosing is contingent upon patient age and therapeutic indication, typically initiated at low doses with titration as necessary. Adults and children aged 12 years and older commonly receive 40–80 micrograms twice daily, with maximum doses up to 320 micrograms twice daily. Pediatric formulations include QVAR for children under five and Redihaler for those under four. The duration of pharmacological activity following inhalation approximates 12 hour.

Routes of Administration:
- **Inhalation:** For maintenance therapy in chronic asthma; not intended for acute exacerbations.
- **Nasal spray:** Utilized in allergic rhinitis and nasal polyposis.
- **Topical:** Applied to treat dermatological conditions such as eczema and psoriasis; for external use only.
- **Oral:** Employed in systemic conditions like ulcerative colitis.

Storage:
BDP should be stored at ambient temperature, shielded from heat and direct sunlight, and must not be frozen or exposed to extreme temperatures. Proper disposal and safeguarding from pediatric access are mandatory to ensure safety.

Adverse Effects
Serious: Include paradoxical bronchospasm, severe throat irritation, vision disturbances indicative of corticosteroid-induced glaucoma or cataracts, and

systemic allergic reactions necessitating urgent medical attention.

Common: Consist of throat soreness or irritation, cough, hoarseness or voice changes, and mild nasal irritation, predominantly related to local mucosal drying or inflammation .30

Budesonide: Pharmacological Profile and Mechanism of Action:

Budesonide (BUD) is a potent, non-halogenated corticosteroid characterized by a high affinity for glucocorticoid receptors and significant topical anti-inflammatory efficacy. It is widely utilized in the treatment of asthma and other inflammatory airway conditions. Upon inhalation, approximately 30% of the administered dose is systemically absorbed, with 17% absorbed directly through the pulmonary route and 13% swallowed and absorbed via the gastrointestinal tract. The swallowed fraction undergoes substantial first-pass hepatic metabolism, resulting in low oral bioavailability.

Clinical investigations demonstrate that both inhaled and oral budesonide exert pronounced anti-inflammatory effects with a favorable therapeutic index relative to systemic corticosteroids such as prednisone. The clinical efficacy is attributed not only to local pulmonary action but also to systemic effects following absorption and potential pulmonary drug recycling .

Mechanism of Action:

Budesonide is a lipophilic corticosteroid that readily permeates cellular membranes and binds to cytoplasmic glucocorticoid receptors (GR). The budesonide-GR complex translocates into the nucleus where it modulates gene expression through two principal mechanisms:

Transactivation: The complex binds glucocorticoid response elements (GREs) on DNA, promoting transcription of anti-inflammatory proteins.

Transrepression: It inhibits pro-inflammatory transcription factors such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), which are instrumental in activating inflammatory gene expression.

Drug Interactions

Budesonide metabolism is principally mediated by CYP3A4, rendering it susceptible to interactions with agents affecting this enzymatic pathway:

CYP3A4 Inhibitors (e.g., grapefruit juice, ketoconazole, itraconazole, ritonavir, indinavir, clarithromycin, erythromycin) increase systemic budesonide levels, heightening risk of corticosteroid-related adverse effects.

CYP3A4 Inducers (e.g., carbamazepine and other anticonvulsants) reduce budesonide plasma concentrations, potentially diminishing therapeutic efficacy.

Dosage

Dry Powder Inhaler (Flexhaler):

- Adults and children aged ≥6 years: initial dose 200–400 mcg twice daily; maintenance dose 200–800 mcg/day; maxi mum dose 800 mcg twice daily (1600 mcg/day).

Nebulizer Suspension:

- Children aged 12 months to 8 years: dose of 0.25–0.5 mg once or twice daily; maximum 1 mg twice daily.

Routes of Administration

Inhalation: Via nebulizer mist for infants and young children; dry powder inhaler for children ≥6 years; metered-dose inhaler combined with formoterol (Symbicort) for older children and adults.

Storage:

Budesonide should be stored at controlled room temperature between 20°–25°C (68°–77°F), protected from light by retaining original packaging or foil pouch. Refrigeration or freezing is contraindicated. It must be kept in a dry environment away from excessive heat and moisture, with storage in bathrooms discouraged. Additionally, the medication must be secured from children and pets to prevent accidental ingestion.

Adverse Effects

Common: Oral candidiasis (white patches in the mouth; mitigated by rinsing the mouth post-inhalation), hoarseness, sore throat, voice changes, headache, nasal congestion, and flu-like symptoms (fever, chills, body aches).

Serious: Increased susceptibility to infections due to immunosuppression, adrenal insufficiency presenting as fatigue, nausea, and weakness, ocular complications including cataracts and glaucoma, osteoporosis with long-term use, growth retardation in pediatric patients necessitating monitoring, paradoxical bronchospasm, and severe hypersensitivity reactions manifesting as rash, swelling, or respiratory difficulty.31

Fluticasone Propionate: Pharmacological Overview and Mechanism

Fluticasone propionate (FP) is a highly lipophilic corticosteroid with potent anti-inflammatory properties, effectively employed in the treatment of allergic rhinitis and asthma. Its lipophilicity facilitates rapid absorption and prolonged retention in pulmonary tissues, enabling strong and selective binding to glucocorticoid receptors (GR) within the airways.

FP exerts multifaceted immunosuppressive effects, including inhibition of T lymphocyte proliferation, suppression of pro-inflammatory cytokines, and

downregulation of cell adhesion molecules induced by tumor necrosis factor-alpha (TNF-α). It attenuates IL-5-mediated eosinophilia and mast cell proliferation, thereby reducing allergic inflammation, mucosal edema, and histamine release.32

Mechanistically, FP binds intracellular glucocorticoid receptors, leading to decreased inflammatory cell activity (eosinophils, mast cells, lymphocytes), reduction of pro-inflammatory cytokines, diminished airway swelling and mucus secretion, and increased beta-2 adrenergic receptor density and sensitivity on airway smooth muscle. These effects culminate in improved bronchodilation, airflow, and symptom control in asthma.33

Drug Interactions

Co-administration with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole) is contraindicated due to risk of systemic corticosteroid toxicity. Concurrent use with NSAIDs may elevate gastrointestinal bleeding risk. Combination with other steroids increases systemic side effects. Aminoglutethimide may reduce FP efficacy.

Dosage and Administration

FP is typically administered via metered-dose inhalers (MDI) or dry powder inhalers (DPI). Adults commonly receive 1–2 inhalations twice daily, with pediatric dosing individualized. MDIs require coordinated inhalation and may be used with spacers, whereas DPIs are breath-activated and incompatible with spacers.

Storage

Store at room temperature in a closed container, protected from heat, moisture, and light. Avoid freezing. Keep out of reach of children. Dispose of expired or unused medication properly.

Adverse Effect

Local: Oral candidiasis, hoarseness, throat irritation, and cough are common local side effects.

Systemic: Prolonged or high-dose use may cause adrenal suppression, decreased bone mineral density, growth retardation in children, ocular complications.334

Mitigating Adverse Effects of Inhaled Corticosteroids:

Proper inhaler technique and appropriate device selection are critical to minimizing side effects of inhaled corticosteroids (ICS). Patients should receive thorough training from healthcare providers, reinforced by instructional materials, to ensure optimal lung deposition and reduce oropharyngeal exposure. The use of spacer devices is beneficial when compatible, as it enhances pulmonary delivery and decreases local side effects; however, certain inhalers (e.g., Diskus, Ellipta, Flexhaler) are incompatible with spacers and should not be used together.Rinsing the mouth immediately after ICS use, followed by expectoration or tooth brushing, effectively reduces local adverse effects such as oral candidiasis and dysphonia.35 Notably, this practice may also mitigate systemic side effects.Employing the lowest effective ICS dose is essential to limit systemic toxicity, including risks of bone loss, infections, and ocular complications. Dose optimization should be individualized with regular clinical assessment to enable dose reduction when disease control permits.Abrupt cessation of ICS can precipitate withdrawal symptoms and adrenal insufficiency; therefore, gradual dose tapering under medical supervision is advised. Continuous monitoring permits safe adjustments, with temporary dose escalation during physiological stress when necessary.Device and corticosteroid molecule selection should be tailored to patient-specific factors, including inspiratory capacity and comorbidities.36 For patients with limited inspiratory effort, soft mist inhalers may be preferred over dry powder inhalers. Molecular differences influence side effect profiles; for example, fluticasone may have a higher impact on hormonal balance and bone density than budesonide.Lastly, lifestyle modifications such as smoking cessation, adequate calcium and vitamin D intake, regular weight-bearing exercise, and balanced nutrition support lung health, enhance ICS efficacy, and reduce systemic corticosteroid complications.37

CONCLUSION:

Asthma is a multifaceted chronic inflammatory airway disease requiring personalized management. Inhaled corticosteroids (ICS) form the cornerstone of treatment by effectively reducing airway inflammation and improving lung function. Proper selection and use of ICS, along with strategies to minimize side effects, are critical for optimal outcomes. Integrating ICS therapy with patient education and ongoing monitoring ensures better asthma control and quality of life.

Inhaled corticosteroids exert potent anti-inflammatory effects through multiple mechanisms, including suppression of pro-inflammatory cytokine production, inhibition of inflammatory cell activation, and modulation of gene expression via glucocorticoid receptor binding. These actions reduce airway edema, mucus hypersecretion, and cellular infiltration, thereby improving airway patency and reducing hyperresponsiveness. ICS therapy has demonstrated consistent efficacy in decreasing asthma symptoms, reducing the frequency and severity of exacerbations, and improving overall lung function and quality of life for patients across a broad spectrum of disease severity.

In summary, inhaled corticosteroids remain the foundation of asthma management, offering powerful anti-inflammatory effects that address the core pathophysiology of the disease. Their judicious use, combined with comprehensive patient education, environmental control, and regular clinical assessment, enables effective symptom control, reduces exacerbations, and improves long-term health outcomes. Continued research into the molecular mechanisms of asthma and the development of novel therapies will further enhance personalized treatment approaches, striving toward optimal disease control and improved quality of life for all individuals affected by asthma.

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