

Complications of Chronic Inhaled Glucocorticoid Therapy in Asthma Treatment

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Abstract:

Asthma is a chronic inflammatory disease of the airways, and its treatment includes the use of inhaled glucocorticoids (ICS). ICS are considered the first-line therapy for controlling asthma symptoms and preventing disease progression. However, long-term use of these medications is associated with the risk of various complications that may affect patients' health. This study discusses the potential complications related to prolonged ICS use, such as oral infections, osteoporosis, hormonal imbalances, and the risk of adrenal dysfunction. The analysis also covers risk factors for these complications, including drug dosage, duration of use, and individual patient characteristics. Additionally, the study proposes strategies to minimize the risk of complications, such as dose optimization, proper inhalation technique, patient health monitoring, and the development of new treatment methods. The aim of this paper is to provide insight into the balance between the benefits of ICS therapy and the potential risks associated with their long-term use.

Keywords: Inhaled glucocorticoids (ICS), Asthma, Long-term complications, Chronic asthma, Oral infections, Osteoporosis, Adrenal dysfunction, Side effects of glucocorticoids, Inhalation therapy

Introduction

Asthma is a common inflammatory disease affecting up to 235 million people worldwide. It is characterized by variable respiratory symptoms, including shortness of breath, wheezing, chest tightness, and cough. Asthma also leads to airflow limitation due to bronchoconstriction, bronchial wall thickening, and increased mucus secretion. [49]

Managing chronic asthma requires avoiding environmental triggers that may cause exacerbations, using short-acting β 2-adrenergic bronchodilators for rapid symptom relief, and taking inhaled corticosteroids (ICS) daily. For patients with moderate to severe asthma, the use of long-acting bronchodilators and biologic therapies may be necessary. [50]

Asthmatic inflammation affects both the central and peripheral airways, including the alveoli. ICS therapy is effective in treating inflammation in the peripheral airways because the inhaled drug can reach these regions and rapidly reduce obstruction. [52]

The heterogeneous nature of asthma has been extensively studied, particularly in severe cases, leading to the identification of more homogeneous groups known as phenotypes. Proper phenotyping of patients allows for the implementation of more specific treatment plans, which is a step toward precision medicine. [51]

The goal of asthma treatment is both to alleviate current symptoms and to prevent disease progression. It is crucial for patients to be able to perform daily activities without limitations. To effectively control symptoms and prevent airway remodeling, inhaled corticosteroids (ICS) are recommended as the first-line therapy. [53]

This study aims to evaluate the complications associated with chronic ICS use, identify risk factors, and propose effective strategies for minimizing these complications.

Chapter 1: Mechanisms of Action of Inhaled Glucocorticoids

Several molecular mechanisms explaining the anti-inflammatory effects of inhaled corticosteroids (ICS) in asthma are currently known. At the cellular level, ICS reduce the number of inflammatory cells in the airways. This occurs through the inhibition of inflammatory cell recruitment to the airways by decreasing the production of chemotactic mediators and shortening the survival time of inflammatory cells such as eosinophils, T lymphocytes, and mast cells in the respiratory tract. [1]

Glucocorticoids increase the production of lipocortin, leading to reduced synthesis of prostaglandins and leukotrienes and inhibition of cyclooxygenase-2 activity. This action helps to reduce neutrophil migration to inflammatory sites and alleviate inflammation. [2]

Chronic use of inhaled corticosteroids reduces both airway inflammation and secondary airway remodeling. A key advantage of ICS is their localized anti-inflammatory effect. As a result, ICS provide beneficial anti-inflammatory action at significantly lower daily doses and with a much lower risk of serious adverse effects compared to oral or systemic corticosteroids. [4]

All inhaled corticosteroids exhibit systemic dose-dependent adverse effects, although these are less intense compared to oral corticosteroids. [5] Numerous studies have demonstrated a gradual reduction in adrenal function with increasing ICS doses, both over short periods and under strictly controlled conditions. [6]

In severe cases of asthma, oral or systemic corticosteroids are preferred. However, long-term use of these corticosteroids is associated with the risk of systemic side effects, such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis, growth inhibition in children, osteoporosis in adults, thinner skin, easy bruising, cataracts, disturbances in carbohydrate and lipid metabolism, changes in body appearance, and mood alterations. [4]

Due to the cost of inhaled steroids, their availability is limited in developing countries, resulting in poorly controlled asthma in patients taking low doses of inhaled steroids for asthma management. A study was conducted to determine the oral steroid doses that would provide equivalent therapeutic effects to ICS doses. A daily dose of 7.5–10 mg of prednisolone appears to be equivalent to a moderate-to-high dose of inhaled corticosteroids. [3]

The systemic effects of ICS result from both the fraction of the drug that is swallowed and absorbed through the gastrointestinal tract—bypassing first-pass metabolism—and the fraction that reaches the lungs and is absorbed. [8]

Chapter 2: Local Complications

Oropharyngeal candidiasis (OC) is a common adverse effect of inhaled corticosteroids (ICS). Based on conducted analyses, the three-year incidence of OC in new ICS users was 7%. The risk of the first OC episode increased with higher ICS doses, longer ICS therapy duration, concurrent use of antibiotics and oral steroids, prescription duplication, prior therapy with both high and low ICS doses, and simultaneous use of oral steroids and antidiabetic medications. [8]

The adverse effects of ICS may result from their local action on the oral mucosa, as only 10–20% of the inhaler dose reaches the lungs, while the remainder is retained in the oropharyngeal cavity. The local deposition of glucocorticoids increases the risk of oropharyngeal candidiasis. [9]

Topical antifungal agents are commonly used to treat most fungal infections. Nystatin ointment can be applied directly to inflamed lesions. [10]

A study involving children with asthma who had been treated with ICS for at least six months demonstrated a significant association between long-term ICS therapy and oropharyngeal candidiasis. [11]

Administration of fluticasone propionate/salmeterol xinafoate (FP/SAL) via a pressurized metered-dose inhaler (pMDI) reduced the risk of developing OC compared to dry powder inhalers (DPI). This may be due to differences in drug deposition within the respiratory tract between the two devices. Studies have shown that FP administered via pMDI has a stronger bronchodilatory effect and achieves better disease control

than FP delivered via DPI, possibly due to better ICS delivery to the lungs and, consequently, lower throat deposition. [12]

Preventive strategies for oropharyngeal candidiasis include maintaining good oral hygiene after inhaler use, using a spacer device, regular dental check-ups, and utilizing mouth rinses. [13]

Voice problems and dysphonia are the most common and troublesome local side effects of ICS, negatively impacting patients' quality of life. [14]

Asthmatic patients require longer pauses between spoken words, produce fewer syllables per breath, and need more time for ventilation outside of speech. [16]

A study on hoarseness/dysphonia involved 313 patients with bronchial asthma using fluticasone propionate (FP) dry powder inhalers (DPI). As a result, 20.4% of FP-DPI users reported hoarseness/dysphonia, with a higher prevalence among women and the elderly—35.8% of female FP-DPI users aged ≥ 65 years reported hoarseness/dysphonia. For patients experiencing hoarseness, particularly women and older individuals, selecting the most appropriate device is crucial to ensuring continued ICS therapy in a comfortable manner. [15]

Another study evaluated voice changes and laryngeal abnormalities in 30 asthma patients using ICS. A total of 53.3% of ICS users experienced dysphonia, mostly mild. Vocal fold erythema was detected in 56.7% of patients, interarytenoid thickening in 56.7%, vocal fold smoothing in 5.3%, and vocal fold atrophy in 5.5%. The study demonstrated that inhaled corticosteroids adversely affect both the function and structure of the vocal folds. [17]

Another study worth mentioning involved 200 adult asthma patients who had been using ICS regularly for at least six months. A questionnaire was used to assess the presence of local adverse effects. As a result, 163 patients (81.5%) reported at least one adverse effect, and 131 (65.5%) experienced at least one symptom daily. Voice and throat-related symptoms were reported by 57 (28.5%) and 154 (77.0%) patients, respectively. The most frequently reported adverse effects were throat dryness, the need to clear the throat, thirst sensation, and hoarseness. [18]

A risk factor for cough immediately after inhalation is the use of a spacer chamber by children instead of another ICS delivery device. A study involving 402 children with asthma treated for at least one month with beclomethasone dipropionate, budesonide, or fluticasone propionate via pressurized metered-dose inhalers and small or large spacer chambers, mainly with face masks, was conducted. Cough after every ICS inhalation was reported in 216 patients (53.7%). The presence of cough was significantly associated with

the duration of therapy and the use of long-acting β_2 -agonists. The type and volume of the spacer chamber, as well as the use of a face mask or mouthpiece, did not influence the occurrence of cough. [19]

Chapter 3: Systemic Complications

Inhaled corticosteroids (ICS) also have an impact on bones. Their action leads to a reduction in bone formation and an increase in bone resorption, which ultimately results in bone mass loss. [21] Corticosteroids decrease osteoblastogenesis, increase osteoblast apoptosis, and limit their ability to form bone. Due to increased production of reactive oxygen species caused by steroids, osteoblast apoptosis occurs. Studies on mouse models have shown that activation of glucocorticoid receptors in osteoblasts results in reduced bone mass, trabecular thickness, and osteoblast count. [22]

A study was conducted within a cohort of elderly individuals taking medications for respiratory diseases. Patients were observed for at least 4 years. There were 9,624 new cases of hip or upper limb fractures and 191,622 age-matched controls (mean age 81). Current use of inhaled corticosteroids did not elevate fracture rates. For upper limb fractures, the rate increased by 12% with every additional 1,000 μg daily dose of ICS. Among patients followed for more than 8 years, the hip fracture rate was only elevated with daily doses above 2,000 μg of ICS. [20]

Suppression of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most important side effects of ICS. Through feedback mechanisms, exogenous cortisol exerts an inhibitory effect on the hypothalamus, pituitary gland, and partially on the adrenal glands. Prolonged suppression leads to a reduction in endogenous cortisol secretion, and the adrenal glands may undergo atrophy. [23]

Adrenal insufficiency is a life-threatening condition that can result from primary adrenal pathology or secondary adrenal disease caused by impairment of the HPA axis. It is caused by a deficiency or impaired action of glucocorticoids. Symptoms of adrenal insufficiency include weakness, fatigue, loss of appetite, abdominal pain, weight loss, and salt cravings. Primary adrenal insufficiency is differentiated from secondary by hyperpigmentation of the skin and orthostatic hypotension. [24]

A study was conducted to determine the incidence of acute adrenal crises associated with inhaled corticosteroid use. 33 patients met diagnostic criteria, including 28 children and 5 adults. Among the 23 children, acute hypoglycemia occurred, with 13 experiencing altered consciousness or coma, 9 having coma and seizures, and 1 patient having coma, seizures, and death. Four adults had a gradual onset of symptoms, with one experiencing hypoglycemia and seizures. Of the 33 patients treated with 500–2,000 $\mu\text{g}/\text{day}$ ICS, 91% received fluticasone, 3% received fluticasone and budesonide, and 6% received beclometasone. [25]

It is known that oral corticosteroids can contribute to hyperglycemia, impaired glucose tolerance, or the development of diabetes in susceptible patients. However, the systemic concentrations achieved during ICS treatment for asthma or COPD patients are considered too low to affect blood glucose levels in most patients. [26]

The negative impact of corticosteroids on glucose homeostasis is attributed to multiple factors, including increased insulin resistance, increased glucose intolerance, reduced β -cell mass due to dysfunction, and enhanced hepatic insulin resistance. Administration of prednisolone to healthy volunteers for 7 days resulted in a 50% reduction in insulin sensitivity.

Corticosteroid-induced hyperglycemia increases the risk of infections, which adversely affects patient prognosis. It is believed that most hospitalized patients taking corticosteroids at a dose of at least 40 mg/day for more than 2 days develop hyperglycemia. Corticosteroid therapy can induce type 2 diabetes and worsen hyperglycemia in patients with pre-existing diabetes. [28]

A clinical-control study involving patients treated with ICS for respiratory diseases showed a 34% increase in the risk of developing diabetes over 5.5 years of observation compared to a control group not treated with ICS. [27]

In another study involving 231 patients with respiratory diseases treated with corticosteroids, 34 patients (14.7%) developed corticosteroid-induced diabetes (S-DM). Risk factors for developing S-DM include older age, high BMI, impaired glucose tolerance before therapy, cumulative dose, and prolonged duration of steroid therapy. [29]

Systemic corticosteroid use is a recognized risk factor for developing posterior subcapsular cataracts. A population-based cross-sectional study on eye diseases confirmed that the use of inhaled corticosteroids is particularly associated with posterior subcapsular cataracts compared to other types of cataracts, likely due to the sensitivity of the lens region to metabolic damage, including that caused by diabetes and oral corticosteroids. It is hypothesized that the mechanism by which corticosteroids cause posterior subcapsular cataracts is the inhibition of sodium-potassium pumps in the lens epithelium, resulting in water accumulation in lens fibers and agglutination of lens proteins. [30]

Another study suggesting that prolonged use of inhaled corticosteroids increases the risk of cataract extraction in older adults was conducted by Edeltraut G and colleagues. Patients who had not used oral corticosteroids but had been treated with inhaled corticosteroids for more than 3 years had three times the risk of cataract extraction compared to patients who had not used inhaled steroids. [31]

Glaucoma, a leading cause of irreversible blindness worldwide, results from the loss of retinal ganglion cells, which is associated with intraocular pressure. Corticosteroids used in eye drops or systemically can increase intraocular pressure. It is believed that this is due to increased resistance to aqueous humor outflow, mediated by glucocorticoid receptors on trabecular cells. [32]

Studies suggest that there is an association between ever use of inhaled corticosteroids and elevated intraocular pressure or glaucoma in individuals with a family history of glaucoma. A family history of glaucoma is a risk factor for developing glaucoma, and patients in this group using inhaled corticosteroids should be referred for periodic ophthalmological consultations. [33]

It is well known that long-term oral corticosteroid therapy adversely affects growth. Systemic corticosteroids are suspected to inhibit the secretion of growth hormone (GH), the activity of insulin-like growth factor-1 (IGF-1), collagen synthesis, and adrenal androgen production. Systemic corticosteroids may reduce the expression of GH receptors and directly inhibit growth plate growth. The issue of growth inhibition during treatment with inhaled corticosteroids remains controversial. [34]

The effect of ICS on linear growth in children with chronic asthma has been evaluated, considering the characteristics of available therapies and treated children (including age, disease severity, and treatment compliance). Low or medium daily doses of ICS result in a change in growth of 0.61 cm from baseline over the course of one year of treatment in children with mild to moderate chronic asthma. Growth inhibition as a side effect of corticosteroids appears to be most pronounced during the first year of treatment, with less pronounced effects in subsequent years. [35]

Chapter 4: Risk Factors for Complications

The side effects of oral corticosteroids are well-documented, whereas less is known about inhaled glucocorticoids (ICS). Observational studies were conducted on an adult group of asthma patients exposed to newly introduced ICS. Short-term use of low doses of ICS was not associated with adverse effects. However, medium to high daily doses of ICS were linked to an increased risk of cardiovascular events, pulmonary embolism, and pneumonia. To minimize side effects, it is important for clinicians to use the lowest effective doses of ICS. [36]

The dose-response curve for clinical response to ICS is relatively flat, in contrast to the steeper dose-response curve for ICS side effects. This suggests that increasing the dose of ICS may yield minimal benefits while being associated with a higher risk of adverse effects.

High doses of ICS show significant immunosuppressive effects, while lower doses primarily have anti-inflammatory effects. It is suspected that high doses of ICS suppress cellular components of the immune

response, such as alveolar macrophages and T lymphocytes, which results in an increased bacterial load in the airways and raises the risk of infections, including tuberculosis. Lower doses of ICS appear to be a better choice, as they primarily exert anti-inflammatory effects, reducing the risk of pneumonia and tuberculosis while having lower systemic absorption. [37]

Patients with chronic obstructive pulmonary disease (COPD), who require long-term use of high doses of ICS, are at risk for numerous local and systemic side effects, including oral candidiasis, cataracts, glaucoma, and osteoporosis. ICS use may also increase the risk of bone fractures, diabetes, and pneumonia. Special attention should be given to elderly patients using ICS, due to the presence of comorbidities and age-related cognitive and psychological issues, which may hinder inhaled therapy. To avoid side effects in the geriatric population undergoing prolonged ICS therapy, it is necessary to monitor the oral cavity, intraocular pressure, and administer bone-protective drugs. The emphasis is placed on using the lowest effective dose of ICS. [38]

In pediatric asthma treatment, it is important to identify the need for step-up therapy in cases of poor control and step-down therapy every three months once good control of asthma is achieved. Dose-dependent side effects are more pronounced in individuals who are also using oral or nasal corticosteroids. [39]

Studies have shown that patients with asthma aged 60 years and older are more likely to use both oral and inhaled corticosteroids compared to patients under 60 years of age. [40]

The medications used to treat asthma are predominantly administered via inhalation to minimize side effects by targeting the lungs. Proper use of inhalers is necessary for effective asthma therapy. The most commonly used inhalation devices are metered-dose inhalers (pMDI) and dry powder inhalers (DPI). In systematic reviews involving asthma patients, frequent inhalation errors were noted among DPI users. The most commonly reported error was failure to perform a full exhalation before inhalation. Other errors included failing to hold the breath after inhalation, improper positioning of the inhaler, incorrect dosing, and improper sealing of the mouth around the mouthpiece. [41]

A study was conducted to evaluate the impact of a single inhalation technique training session on the frequency of inhalation errors in asthma and COPD. One session of inhalation technique training resulted in a reduction in the number of inhalation errors, but the effect was temporary and did not influence the course of asthma or COPD. [42]

The response to asthma treatment with glucocorticoids varies significantly between individuals. The role of genetics in the variability of response to ICS therapy in asthma has been studied. A study investigated the relationship between long-term changes in lung function and single nucleotide polymorphisms in genes

important for the biological actions of corticosteroids. Differences in the corticotropin-releasing hormone receptor 1 (CRHR1) gene were associated with an enhanced response to therapy. [43]

Chapter 5: Strategies for Minimizing Complications

The safety profile of ICS appears to be dose-dependent, with the occurrence of serious adverse effects associated with higher doses, while the risk is lower when lower doses are used. The flat dose-response curve justifies the minimal clinical benefit gained by increasing the dose of the drug, while the risk of adverse effects rises, as described by the steeper dose-response curve for systemic side effects. Higher doses of ICS show strong immunosuppressive effects, while lower doses primarily have anti-inflammatory effects, which further supports the strategy of using lower doses of ICS. [37]

Problems with inhalation technique are very common and can lead to inadequate symptom control. Written instructions are often ineffective, while direct or video demonstrations with a doctor or trained nurse are more effective in ensuring proper inhalation technique and adherence to therapeutic recommendations. [45]

The most commonly used inhalation devices are metered-dose inhalers (pMDI) and dry powder inhalers (DPI). Modern pMDI inhalers use hydrofluoroalkane (HFA) propellants, which replaced the previously used chlorofluorocarbons (CFC). HFA propellants create an aerosol stream with less force and higher temperature compared to CFCs. These properties, combined with a smaller outlet in most new HFA inhalers, result in a slower release of the aerosol, which facilitates the inhalation process and reduces irritation in the oral cavity.

HFA inhalers can now deliver the drug in the form of a solution, rather than a suspension as with older CFC devices, eliminating the need to shake the inhaler before use. Breath-actuated pMDIs, activated by a spring that responds to airflow during inhalation, are particularly helpful for patients who have difficulty synchronizing their inhalation. Valve holding chambers (VHC) help eliminate problems related to inhalation coordination, as well as reduce the speed and decrease the aerodynamic diameter of aerosol particles entering the airways. Larger particles settle on the walls of the VHC, while smaller ones evaporate, leading to their fragmentation. As a result, more aerosol reaches the peripheral parts of the respiratory system. [44]

Modern innovations in DPI engineering and chemistry have enabled the development of newer generation inhalers activated by low inhalation flow rates (~30 l/min or less), which ensure better drug deposition in the lungs (>40%). Dry powder inhalers with small particle sizes that can be inhaled at low flow rates and achieve high lung deposition (>40%) have also been developed. [46]

Current asthma treatment guidelines recommend the use of long-acting β 2-agonists (LABA) in combination with inhaled corticosteroids (ICS) in patients whose ICS alone do not provide adequate disease

control. This approach allows simultaneous targeting of two key asthma mechanisms: bronchoconstriction and the inflammatory process. Studies have shown that the ICS/LABA combination therapy results in better symptom control in asthma and COPD, as well as a reduction in the number of severe exacerbations. Preclinical study results confirm that ICS and LABA exhibit additive, complementary, compensatory, and synergistic actions in controlling inflammation and airway and lung remodeling. [47]

Triple therapy, consisting of inhaled corticosteroids (ICS), long-acting β 2-agonists (LABA), and long-acting muscarinic antagonists (LAMA), is used in the treatment of severe asthma and stands out for its favorable safety profile. The addition of LAMA to the ICS/LABA combination and the possibility of adjusting the ICS dose make this therapy a versatile pharmacological solution, suitable both for patients with difficult-to-control asthma and for those with moderate disease. [48]

Summary

Chronic use of ICS in asthma treatment is associated with a range of potential complications. The local anti-inflammatory effect of ICS is crucial in managing symptoms and reducing the risk of severe exacerbations. However, their long-term use can lead to both local and more serious systemic adverse effects such as osteoporosis, HPA axis disturbances, adrenal insufficiency, steroid-induced diabetes, cataracts, glaucoma, and growth inhibition in children and adolescents. Additionally, inhalation technique issues can increase the risk of improper drug deposition in the lungs. It is important for clinicians to use the lowest effective doses of ICS and monitor patients for adverse effects in order to minimize the risk of complications and improve asthma treatment outcomes.

Author's Contribution Statement

Conceptualization, Natalia Furlepa and Monika Brzozowska; methodology, Natalia Wieczorek-Durdzińska and Robert Rzenno; software, Marcelina Matuszewska; check, Monika Brzozowska, Natalia Furlepa and Natalia Sidz; formal analysis, Wiktoria Jedlikowska; investigation, Natalia Wieczorek-Durdzińska and Robert Rzenno; resources, Marcelina Matuszewska and Natalia Sidz; data curation, Wiktoria Jedlikowska and Magdalena Tomaszewska; writing - rough preparation, Karolina Wojciechowska and Natalia Furlepa; writing - review and editing, Natalia Furlepa; visualization, Karolina Wojciechowska ; supervision, Natalia Furlepa; project administration, Monika Brzozowska

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