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A Guide to Inhaled Corticosteroids for Asthma Management

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Abstract

Inhaled corticosteroids (ICS) are the most effective controllers of asthma and are also used to treat many other chronic inflammatory diseases that affect the bronchial mucosa, such as chronic obstructive pulmonary disease and rhinitis. ICS switch off multiple activated inflammatory genes through transcriptional control of all of these genes and also through reversing histone acetylation, which is achieved through recruitment of histone deacetylase 2 (HDAC2) to the activated inflammatory gene complex. This is initiated by the corticosteroid binding to the glucocorticoid receptor-alpha, which rapidly enters the cell nucleus, such as with the activated inflammatory gene macrophage migration inhibitory factor (MIF) gene in asthma.

The suppression of airway inflammation is important since it reduces irreversible airway remodeling and prevents progression of the disease. Airway inflammation is primarily a T-helper type 2 (Th2) lymphocyte-driven eosinophilic inflammation in atopic asthma, which is also associated with mast cells, and more recently has been shown to have a role for group 2 innate lymphoid cells that mediate type 2 inflammation in patients with severe asthma. Airway inflammation increases the number of airway inflammatory cells, which can release proinflammatory mediators, cytokines, and chemokines that increase airway hyperresponsiveness by acting on airway smooth muscle, make the airway wall swell, which causes the airway narrow, and increase airway mucus secretion, which blocks the airway (J. Barnes, 2010).

Keywords:-Inhaled corticosteroids (ICS) are the most effective controllers for the treatment of asthma. Inhaled corticosteroids are the most effective controllers for the long-term treatment of asthma; they suppress inflammation in asthma, reducing symptoms and exacerbations, and preventing fixed airflow obstruction and chronic airway remodeling. Inhaled corticosteroids reduce the multiple activated inflammatory genes in asthma by switching off through the

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recruitment of histone deacetylase 2 by the activated glucocorticoid receptor. This is associated with a reversal of histone acetylation and with suppression of activated inflammatory genes such as interleukin-8 and inducible nitric oxide synthase with prevention of recruitment of inflammatory cells in asthma. Treatment with inhaled corticosteroids added to as-needed short-acting β2 -agonists, in a similar dose response, reduces airway hyperresponsiveness, an early and characteristic feature of asthma, as well as controlling asthma symptoms.

A combination of inhaled corticosteroids and long-acting β2-agonists is used for the persistent treatment of asthma. Physician-diagnosed asthma affects approximately 7% of adults and children in western Europe and the USA, with a similar prevalence in the inner cities of the US and the UK. Asthma is increasing in prevalence and its control is often poor even in economically developed countries, with over half of all patients reporting symptoms in the past year. Asthma accounts for significant morbidity and is associated with about 200 000 deaths worldwide each year, particularly in less economically developed countries. Inhaled corticosteroids (ICS) are the main controller therapy, and as such they are the most effective and widely prescribed treatment for asthma (J. Barnes, 2010).

1. Introduction to Asthma

Asthma is a common, often severe chronic inflammatory disease of the airways. It is associated with a reversible airway narrowing to various triggers like inhaled allergens, respiratory viruses, or cold air. It affects all age groups and causes significant morbidity and mortality globally. Asthma is characterized by airway inflammation, airway obstruction, and airway hyperresponsiveness (J. Barnes, 2010). Airway inflammation results in swelling of the airways and secretion of mucus. In addition, the muscle that surrounds the airways goes into spasm, especially to triggers. Asthma symptoms range from mild to severe and spirometry is used to diagnose asthma. Treatment options for asthma are managed at three levels: lifestyle changes, medications, and at the level of medical intervention. The lifestyle changes mostly consist of treating triggers like allergens and tobacco smoke. Medication is managed through inhaled corticosteroids (ICS) usually prescribed by a physician. In case the medications do not work at an optimal level, the patient moves to step up medication.

2. Understanding Inhaled Corticosteroids

Inhaled corticosteroids (ICS) are the most effective controllers of asthma (J. Barnes, 2010). They suppress inflammation mainly by switching off multiple activated inflammatory genes through reversing histone acetylation by recruiting histone deacetylase 2 (HDAC2) to the activated inflammatory transcription complex. This effect appears to be gene selective because

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corticosteroids do not inhibit housekeeping genes that are not activated by inflammatory stimulation. ICS also restore histone deacetylases to the activated inflammatory cells, which are deficient in asthma and further suppress activated inflammatory genes. By suppressing airway inflammation, ICS reduce airway hyperresponsiveness and control symptoms of asthma, particularly reducing nocturnal symptoms. ICS are now first-line therapy for all patients with persistent asthma, controlling symptoms and preventing exacerbations.

Inhaled long-acting β2 -agonists were approved as add-on therapy to ICS in severe asthma. They improve asthma control rather than asthma severity, as defined by global initiative for asthma guidelines, and there is little benefit of adding LABAs to ICS or increasing the dose of ICS in patients with mild or well-controlled asthma. However, failure of ICS to control mild and moderate asthma is usually because of poor compliance, and combination inhalers can improve compliance. Thus, combination with ICS to improve asthma control is recommended by the guidelines which have recently revised their statement to recommend ICS plus LABA as preferred step for moderate asthma. Combination inhalers are commonly used once-daily available and further improve compliance over two separate inhalers. Combination inhalers control asthma at lower doses of corticosteroids and improve effectiveness and reduce systemic side effects. For long time, ICS have been given mostly budesonide, fluticasone or beclomethasone and this plan has improved overall compliance as patients receive refills and comply more effectively.

3. Mechanism of Action

Asthma is a common chronic disorder of the airways which is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial spasm and bronchial hyperresponsiveness. Inhaled corticosteroids (ICS) are the most effective controllers of asthma, with the most effective ICS being fluticasone propionate and beclomethasone dipropionate. The action of corticosteroids is characterised by entry into cells and binding to cytoplasmic receptors which pass to the nucleus and bind to the promoter region of activated inflammatory genes inducing the production of anti-inflammatory proteins. ICS and oral corticosteroids (OCS) are similar with respect to their ability to suppress markers of airway inflammation (J. Barnes, 2010). Plasma cortisol levels peak during the early morning and this is also the time for a peak in asthma. Morning OCS dosing is associated with a better clinical response when given to patients in the evening. Differences noted between ICS and OCS caused by circadian changes in the regulation of inflammatory gene expression in asthmatic airway epithelium. This is difficult to reverse in COPD, as macrophages and T lymphocytes express only low levels of the glucocorticoid receptor and so the anti-inflammatory effects of corticosteroids are much reduced.

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Inhaled fluticasone propionate (FP) using a Diskus™ inhaler can reduce the long-term decline in lung function and improve health status. Furthermore, FP can suppress the conversion of sputum eosinophils to eosinophilic engulfed eosinophils, which are more resistant to the effects of corticosteroids. It was shown that FP suppressed the increase in eosinophilic engulfed eosinophils after allergen inhalation challenge, an effect not seen after placebo.

ICS suppress inflammation in the airways mainly by switching off multiple activated inflammatory genes, including both inflammatory mediators and activated inflammatory transcription factors. The activated state of inflammatory genes in their promoters is characterised by increased chromatin acetylation, reversibly regulated by histone acetyltransferases (HAT) and histone deacetylases (HDAC). The entry of corticosteroids into cells is probably regulated by the CysLT1 transmembrane protein and drug entry and nuclear translocation dependent on an intact cytoskeleton. Once corticosteroids have entered the cytoplasm, the lipophilic drug–receptor complex exits rapidly enter the nucleus without nuclear chaperones. Transcription of inflammatory genes is regulated by the activation and reversible binding of activated inflammatory transcription factors. Glucocorticoid–receptor complexes bind to activated inflammatory transcription factors and induce the production of proteins that translocase to the activated gene promoter and prevent the binding of transcriptional coactivators and HAT. Reversible regulation of histone acetylation appears to be a major mechanism for switching off activated inflammatory genes, indicating the importance of HDAC2. There is good evidence that ICS treatment reverses histone acetylation at the site of the promoters of inflammatory genes that are switched off by corticosteroids through the recruitment of HDAC2. The most common adverse effects of oral corticosteroids are osteoporosis, growth defects in children, increased adrenal gland suppression, easy to skin thinning and petechiae, cataracts, diabetes mellitus, and hypertension. As ICS use is much less systemic corticoids than oral corticosteroids, these complications are relatively less observed and the most frequent is oral candidiasis. There are 2 commercially available ICSs in Japan: DPI, Fluticasone Propionate Dry Syrup and MDI, Fluticasone Propionate Gasfine Inhalation. FPDS, already being used in patients with bronchial asthma, is reported to be useful for prophylactic therapy against fever and white blood cell infiltration in bronchoalveolar lavage fluid of viral antigen sensitized mice by suppressing cytokines such as transforming growth factor beta-1 and interleukin 13.

4. Indications for Use

Inhaled corticosteroids (ICS) have been the cornerstone of asthma management for a long period of time and are the most effective controller medication for the long-term treatment of children and adults with mild, moderate and severe persistent asthma (M. C. van Aalderen & B.

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Sprikkelman, 2010). Also it can be used short-term before exposure to asthma triggers and as-needed to prevent exercise-induced bronchoconstriction. Systemic corticosteroids, not to be confused with ICS, are a different class of corticosteroids and should not be used for long-term or acute management of asthma. Systemic side effects associated with ICS are uncommon and are primarily dependent on the asthma doses delivered daily. ICS once constituted continue to be first-line maintenance therapy for paediatric asthma, although their use has declined in children in recent years, possibly due to concerns about side effects, even though these are primarily associated with the high doses used for many years for the treatment of adults. In adults and children, side effects due to ICS use are primarily seen at high doses or levels of exposure and are uncommon at low doses. There is a concern among the public that ICS is abused by athletes to improve performance. Indeed, WADA has classified ICS as a class S9. Glucocorticoids and β2-agonists according to the Anabolic Agent List of Banned Substances. Therefore, athletes must apply for a Therapeutic Use Exemption (TUE) to allow the use of these substances for asthma. Asthma prevalence and treatment per se are not necessarily performance-enhancing and the prevalence of asthma medicines on the Prohibited List often appears quite low; however, with the advent of the ADAMS system in 2010 it is likely that more medication uses will come under scrutiny.

5. Types of Inhaled Corticosteroids

Commonly used inhaled corticosteroids (ICS) in Australia are beclometasone dipropionate, budesonide, fluticasone propionate, and ciclesonide (M. C. van Aalderen & B. Sprikkelman, 2010). In New Zealand, ciclesonide is not funded and is less commonly used. Beclometasone dipropionate and fluticasone propionate are both halogenated corticosteroids so are stronger than the non-halogenated counterparts. All provide similar levels of anti-inflammatory effects but have differences in potency, absorption and metabolism - thus requiring different doses. Low doses of ICS are effective in the treatment of children with mild persistent asthma and can be used long term to maintain asthma control.

Use of inhaled combination therapy with long acting beta-agonist (LABA) and an ICS may be more effective than ICS mono-therapy at improving asthma symptoms and lung function and reducing the risk of exacerbations. The most commonly used LABA with ICS combination metered dose inhalers in Australia, New Zealand, UK, US and Canada are (beclometasone/formoterol) and (budesonide/eformoterol) and (fluticasone propionate/salmeterol) (Latorre et al., 2015). There are some ICS/LABAs with combination brands of ciclesonide/formoterol and beclometasone/formoterol, but at the time of writing, these are not commonly used in Australia and New Zealand, and in New Zealand are also not funded.

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Some children who are responding poorly and fulfill the criteria to step up (mainly peak flow < 80% predicted) may be given a 5-7-day course of prednisolone. If control is not achieved with the increase ICS and the above pharmacological criteria are met, an ICS/LABA combination inhaler should be added. This step should include a review of adherence, inhaler technique, and comorbidities which may increase the risk of asthma or exacerbation. The addition of treatment should have a clear aim with a review of response in 2-4 weeks if treatment is stepped up.

5.1. Beclomethasone

Inhaled corticosteroids (ICS) are generally accepted as the most important anti-inflammatory treatment for asthma. They are currently recommended as first-line therapy for the treatment of asthma. Beclomethasone is one of the oldest available formulations. Established with the improvements made to the original formulations of dry powder inhalation (DPI) and hydrofluoroalkane propellant metered dose inhalation (HFA-MDI), it is still largely used to treat asthma.

It is strongly recommended to adjust asthma treatment based on day and night symptoms and measurement of lung function impairment. It is suggested that a stepwise approach should be used, proposing a five-step approach with different modifications of treatment based on the level of asthma control of a given patient. Treatment should start at the appropriate step based on the patient's level of asthma control and it can be adjusted as you consider appropriate and as your patient's level of control of asthma changes. The beneficial effects of inhaled corticosteroids (ICS) in combination with different types of bronchodilators are well documented. In case of patients treated with ICS, alone or in combination with other controllers, an alternative dual bronchodilator treatment with a combination of a long-acting β2-adrenoceptor agonist (LABA) and a long-acting muscarinic antagonist (LAMA), can be taken into account. Alternatively, the treatment can be stepped up to a high dose beclometasone dipropionate/formoterol fumarate (BDP/FF) fixed dose combination of 100/6 μg. This combination is extrafine and in comparison to others, has the higher beclometasone dipropionate formulation containing the same dose of formoterol fumarate (6 μg) (Corradi et al., 2016). The evidence supporting the step-up treatment with inhaled high-strength BDP/FF via NEXThaler DPI in new or previously treated but not well controlled asthmatic patients is scarce. Four clinical studies published in the last year evaluated the efficacy and safety of the high-strength BDP/FF 100/6 μg extrafine beclometasone dipropionate/formoterol fumarate formulation, administered via NEXThaler DPI, compared with either another 100/6 μg high-dose BDP/FF fixed combination, extrafine formulation to another formulation, or with BDP 100 μg plus a separate bronchodilator as 12 μg formoterol fumarate, administered concurrently via the Nexthaler DPI plus another inhaler.

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5.2. Budesonide

In the 1960s, researchers at the Swedish pharmaceutical company designed a novel series of potent non-symmetrical 16α, 17α-acetal corticosteroids for an antiinflammatory drug. The lead compound, budesonide, was found to have a topical selectivity (ratio of inhibitory concentration 50% on human synoviocytes to mean inhibitory concentration to human skin fibroblasts) several-fold better than budesonide and other dermal steroids. In an early human skin-blanching study, epidermal versus systemic potency of budesonide was found to be approximately 2.5-fold superior to that of budesonide and 10-fold superior to that of the more potent dermal steroid, triamcinolone acetonide. The first patent application for budesonide and related compounds was filed in 1972 and budesonide was selected as a candidate drug by Astra AB in 1974, with asthma as the primary indication. Positive initial study results led to the approval of budesonide in 1981 by the Swedish regulatory authority for daily maintenance treatment of asthma. In the U.S. and other countries, budesonide was subsequently approved for the treatment of asthma, as well as allergic rhinitis and chronic obstructive pulmonary disease (COPD). Additional pulmonary indications followed for budesonide in combination with formoterol in a single inhaler, and for budesonide for oral inhalation. All budesonide pulmonary drug formulations are wet-milled micronized, based on the development of a specially designed jet mill for this purpose. Budesonide was delivered via a pressurised metered-dose inhaler (pMDI), the first marketed ICS as a patented, solution-based HFA system. Dose-dependent improvements in peak expiratory flow (PEF) were demonstrated for daily doses of 400–1600 μg, with the two highest doses equivalent to beclomethasone dipropionate at 1500 μg and fluticasone propionate at 1000 μg . As expected, the initial magnitude of the PEF increase was greater when budesonide was initiated at a higher severity stage. Early intervention independent of severity and disease duration also led to a later reduction in exacerbations. It was concluded that these studies supported early intervention with ICS after the initial onset of symptoms. In turn, these studies contributed to an increased early use of ICS in asthma of all severities and were important factors in the recommendation of ICS as first-line therapy in asthma guidelines. All new studies, however, were conducted with a follow-up period of less than a year, and medium-term or long-term real world research is lacking so far. An important factor in the real world is the use of ICS (Long-acting β2-agonists (LABAs) as preventer) in fixed-dose combinations, as evidenced by an increased usage post-U.S. guideline updates in 2007 and 2009. Amplified risk mitigation efforts to reduce the discrete risk associated with LABAs due to salmeterol mDA and a potential but undefined relative hazard with formoterol and budesonide were essential. Major technological advances in domestic and portable devices for inhaled delivery of drugs (pressurized metered-dose inhalers, dry powder inhalers, and soft mist inhalers) began in the late 1990s and early

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2000s. The first device for the lung delivery of budesonide was a conventional pMDI, with each actuation containing 225 μg. Subsequently, a powder inhaler device Standard Air was developed, consisting of a mixture of budesonide micronized to be within the particle size range of 1 to 7 mm (66%) and medium-chain-length glycerides (33%); it delivered 200 μg per inhalation. Nonetheless, lung deposition in six healthy subjects was determined to be only 6.1±1.7%, the pooled value for individual devices varying from 2.4 to 13.8%. A comparison between the original suspension pMDI and the newly developed budesonide DPI found that lung deposition was approximately doubled with the DPI. Two 4-week studies with a cross-over design in asthmatics compared the impact of Freon-free pMDI and Turbuhaler formulation inhaled budesonide. One study was conducted with single doses from 400 to 1600 μg in total and the other with free doses from 700 to 3200 μg in total. In each of the both studies, dose-dependent improvements in the peripheral lung resistance (R5), in the peripheral-reactance area, and in airway responsiveness to methacholine, supported a therapeutic dose-response relationship. Placebo had no significant effect on these endpoints. Consistently in both studies, the overall effects of each dose level on R5 at methacholine doses of 1 mg/ml in the single-dose study and 0.2 mg/ml in the free-dose study were already statistically significant from the first dose. Subsequent studies confirmed these findings, inhaled delivery of budesonide improved the therapeutic ratio of the compound, and higher efficiency of lung deposition aided a better understanding of the mechanisms underlying the clinical efficacy of budesonide in the prevention of asthma symptoms. Nine efficacy studies of 12 weeks duration in moderate-to-severe persistent adult or pediatric asthma patients were published. Another high dose ranging study with 13 treatment groups and rescue albuterol found significant improvements versus placebo with the application the highest budesonide dose of 3200 μg once daily. In the overall adjudication, budesonide pMDI was considered effective while is well tolerated. Also in this view, these newly accessible study reports help to evaluate the benefit:risk ratio inherent of the use of budesonide in the management of all levels of asthma severity and confirmed the profile of the substance as an effective and well-tolerated ICS. Overall, this review article is based on and updated an earlier overview evaluating the benefit:risk profile of budesonide in the management of obstructive airways disease. A very limited amount of early study reports and other relevant OLS thought to be first will be considered.

5.3. Fluticasone

Fluticasone furoate is a once-daily inhaled corticosteroid present in the Veramyst® product for the treatment of allergic rhinitis. It recently received FDA approval as an inhaled corticosteroid for asthma in the ArmonAir™RespiClick® dry powder inhaler device. It is available in doses of 100 μg and 200 μg, with the dose recommended by the FDA being between 100 μg and 200 μg

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once daily in the evening. This advice breaks down the results of an integrated safety and efficacy analysis from 12 randomized, double-blind, parallel-group controlled trials examining asthma symptoms, acute asthma attacks, serious asthma events, vital signs, continuous pulse oximetry, treatment-emergent adverse events, discontinuations due to treatment-emergent adverse events, serious treatment-emergent adverse events, pneumonias, and oral candidiasis. The intent is to offer clinical providers a broad level overview of the full body of safety and efficacy data available on this topic in up-to-date, clear, and succinct language. These data support the use of once-daily fluticasone furoate 100 μg or 200 μg in adult and adolescent asthma patients.

Medical subject heading (MeSH) terms utilized for each trial involved "fluticasone furoate" or different spellings and variants of the drug name. A total of 1,747 papers were extracted, and doubling-up on clinical trials necessitated an additional 64 exclusions, resulting in a total of 39 unique papers. After further screening, ten reports of twelve trials were discovered that met the inclusion/exclusion criteria. Subsequently, correspondence with GlaxoSmithKline resulted in added access to the Veramyst development programme manuscripts - a sum of eleven. Two additional relevant abstracts were found in the search results and included them in OPERA and PRISMA flowchart. Ashfield Drug Discovery Communications performed all assessments because they had no association with the study sponsors (M. O'Byrne et al., 2016).

5.4. Mometasone

Over the past two decades, inhaled corticosteroids (ICS) have been demonstrated to be the most effective treatment for persistent asthma. ICS have consistently been shown to be safer when compared to chronic systemic corticosteroids. The mechanism of action of ICS in asthma is still not entirely known but involves a variety of cellular effects. The proposed primary mechanism is the genomic interaction of the steroid with the glucocorticoid receptor followed by modulation of gene expression to produce anti-inflammatory proteins, inhibition of proinflammatory proteins, and suppression of the release of proinflammatory cellular mediators. The net effect is inhibition of cytokine release, including IL-4, IL-5, IL-6, IL-8, IL-13, and TNF alpha, and a decrease in inflammatory mediator release. Other effects of ICS include the inhibition of the late-phase allergic response and decreasing eosinophil and mast cell recruitment in the late phase via inhibiting the release of chemotactic factors and adhesion molecules (A Tan & Corren, 2008).

In addition, ICS suppresses the expression of adhesion molecules on endothelial cells, thereby disrupting eosinophil vascular adhesion, tissue migration, and activation. In some in vitro models, ICS blocks the upregulation of eosinophil function. These cellular effects translate

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clinically into significant improvements in pulmonary function and asthma symptoms as well as reductions in exacerbations requiring oral corticosteroids, emergency room care, and hospitalization. A compensatory feature of ICS therapy is the suppression of the recovery of the inflammatory response of the bronchial wall following allergen challenge (Song et al., 2021).

6. Dosage and Administration

Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of cough, shortness of breath, wheezing, and chest tightening. In individuals with asthma, the airways are reactive to multiple stimuli, and may become more narrowed, particularly in response to inflammation. In this condition, the level of inflammation may be higher than during asymptomatic periods, even though lung function is normal. The use of inhaled corticosteroids is the most effective method for treating the underlying inflammation, as it targets the pathophysiological processes responsible for asthma symptoms. In patients with asthma in whom control is not achieved using low or medium doses, elevated doses of inhaled corticosteroids are required. Singularly, elevated doses of inhaled corticosteroids are less effective than lower doses combined with other asthma control medications. Combination inhaled corticosteroids + long acting beta-2-agonists are more efficacious at reducing exacerbations when compared with higher doses of fluticasone propionate. In combination products, equivalences between agent doses are never straightforward. For example, the potency of fluticasone propionate is about twice that of beclomethasone dipropionate or budesonide and about sixteen times that of flunisolide. Fixed combination products are useful in individuals known to have bad inhaler technique or a poor acceptance of the need for using multiple devices. Better control may be obtained by the use of leukotriene receptor antagonists, especially in patients with asthma exacerbated by aspirin or other cyclo-oxygenase inhibitors. Fixed dose long acting beta-2-agonists + inhaled corticosteroid combinations are more effective in chronic obstructive pulmonary disease than higher dose inhaled corticosteroids alone. Inhaled anticholinergics are an alternative therapy to achieve bronchodilation and are particularly useful in reducing the number of severe exacerbations in patients with moderate-severe asthma. Biomarkers of eosinophillic inflammation may help in deciding when to lower corticosteroid doses (Issa-El-Khoury et al., 2015).

7. Common Side Effects

Inhaled corticosteroids have proven to be effective in the management of patients with chronic asthma. Its side effects are often mild when compared to long term systemic corticosteroid therapy, but they remain an important complication probably underestimated by physicians. The local side effects of inhaled corticosteroids: current understanding and review of reported

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literature. The effects of a daily dose of inhaled corticosteroid therapy on exacerbations treated with oral steroid in patients with bronchial asthma managed in primary care. The local side effects of inhaled corticosteroids: current understanding and review of reported literature. Adherence to low dose inhaled corticosteroid treatment is an increasing issue, locally leading to anxiety, mid-point reassessment, and careful discussion of the conundrum of moderating or increasing ICS dose. It is necessary to take the step of reviewing the methodology to see if it is possible that the findings could have been different but unavoidable in the circumstances (Ribeiro Pinto et al., 2013).

8. Long-term Management of Asthma

Asthma is a chronic inflammatory disorder of the airways that is characterized by reversible airway obstruction and hyper-responsiveness of the airways in response to environmental triggers such as allergens, irritants, or changes in the environment. The treatment of chronic asthma is based on anti-inflammatory therapy with inhaled corticosteroids and inhaled long-acting b2-agonists or bronchodilator therapy with inhaled short-acting b2-agonists and anti-cholinergics.

Inhaled corticosteroids have been available for the treatment of asthma for many years and several drugs with different pharmacokinetic properties and potencies are currently in clinical use. Inhaled corticosteroids are very effective in controlling the underlying inflammation of asthma, especially when used by inhalation. There has been concern, however, generated by studies that have suggested that the use of inhaled corticosteroids is associated with death from asthma, presumably because of the suppression of adrenal function and an increase in susceptibility to severe asthma attacks.

Long-acting b2-agonists, in combination with inhaled corticosteroids, can improve both the symptoms and lung function of patients with asthma who are inadequately controlled on inhaled corticosteroids alone. The use of inhaled corticosteroids has been associated with a reduction in bone mineral density, although the incidence of fractures does not appear to be increased. The long-term consumption of systemic corticosteroids is associated with significant risks such as osteoporosis, osteonecrosis, and diabetes. It is not known, however, whether inhaled corticosteroids can affect bone mineral density when used long-term in patients with asthma who are compliant with their therapy. The use of inhalers with added spacers has been recommended as the optimum way of using inhaled therapy in asthma, especially in children and in the elderly (J. Barnes, 2010).

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9. Patient Education and Adherence

Patient education in bronchial asthma is to provide the patient with suitable information and training so that the patient can keep well and adjust according to a planned medication. A continuous asthma project including health education achieved a reduction in asthma-related costs and the severity of asthma. The effects on knowledge of the disease and self-management of asthma were evaluated in addition to the indirect and direct costs. The purpose of the study was to investigate patient education and drug compliance in bronchial asthma. Patient education was accomplished by describing bronchial asthma using simple audiovisual means and by employing self-action plans. The effect of this education was studied by the direct observation of adherence to treatment with inhaled budesonide in 252 adult patients suffering from bronchial asthma. Noncompliance was shown in 149 patients. Valid educational program for asthmatics can improve the knowledge and understanding of the disease, and enable patients to understand how they may look after themselves by careful evaluation of their own symptoms and respiratory function. Compliance with remaining in the program is more than 80% of the visits. Meanwhile, the education intervention provided enabling care via regular follow-up to ensure all asthma clinic patients received treatment package, thus resolved the difficulty in seeking care and guidance to have better self-care and awareness. In total, more than 95% patients were prescribed inhaled steroids. Both findings were in agreement with what were found in the study.

10. Monitoring Asthma Control

After daily maintenance therapy begins, the most widely recommended assessment of control is the use of a consistent and simple monitoring strategy. This includes morning and evening assessments of symptoms, peak flow readings twice a day, self-assessment of lung function with a peak flow meter, assessing the need for rescue treatment, inhalation technique and adherence (L. Rottier et al., 2015). Developing a correct inhalation technique is very important. Even if the correct technique is used, factors like inspiration speed, strength and residual air volume in the lungs may make a difference in drug delivery (L.P. Brand et al., 2015). Therefore, regular follow-up is needed to check and correct the technique. A major failure in the treatment of asthma is poor adherence to the prescribed treatment regime. Adherence can only be improved if regularly assessed. Moreover, there is a need to check whether prescribed drugs are actually well tolerated, and whether side effects attributed to pharmacological treatment are not manifestations of poor adherence to treatment. As with other chronic diseases, it is desirable to periodically take a step back and look at the whole picture of the patient's care. This is why patients with asthma should be re-assessed every 3-6 months (6 months for better controlled asthma) after the initial setting of treatment to review the long-term asthma management plan regularly and to ensure that the treatment plan is achieving disease control. To view the long-term efficacy of asthma

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management and to identify inadequate and/or defective strategies, asthma control and pharmacological treatment should be reviewed periodically. Regular monitoring of asthma control in children is necessary so that treatment can be stepped up when asthma exacerbations appear or to avoid the dangers of over-treatment. However, exacerbation in children with asthma do sometimes go beyond their understanding and result in the delay in taking appropriate action, such as seeking medical help. Hormonal and other changes in puberty will also affect the natural course of asthma. Moreover, drug treatment, drug metabolism and inhalation techniques may not always remain the same in this age group.

11. Role of Spacer Devices

Asthma is one of the most common chronic diseases worldwide, and a major cause of morbidity and mortality. Inhaled corticosteroids are the most effective treatment for asthma and are recommended for all patients with persistent asthma. To maximize the benefits of inhaled corticosteroid therapy, it is necessary to ensure that patients receive maximally effective doses of their inhaled corticosteroids. This requires that patients use correct inhalation technique to overcome the considerable nonuniformity with which inhaled corticosteroids are deposited in the airways. The aim of this text is to provide clear instructions on how to use inhaled corticosteroids in order to maximize lung delivery.

A spacer device is a chamber which traps the drug cloud after actuation of the metered dose inhaler can. Once the drug has been actuated and is inside the chamber, the patient can inhale at his or her own pace from the spacer. The advantages of using spacer devices are they slow down the aerosol cloud as it emerges from the metered dose inhaler, reduce the impact of hand–breath coordination problems, have a longer propellant evaporation time that reduces particle size and improves lung deposition, filter out larger aerosol particles, and reduce oropharyngeal impaction/deposition and local side-effects. Using a spacer device with a metered dose inhaler can rapidly improve respiratory function and has been shown to be the lower cost strategy to achieve similar gains in both lung function and health status compared to multiple other interventions.

12. Comparative Effectiveness

One type of research is focused on efficacy studies designed to determine how well a product or treatment works under optimal conditions; this is typical of industry-sponsored randomized controlled trials (RCTs). Another type of research is focused on effectiveness, a broader evaluation of the value of a product or treatment for a patient that considers how well patients respond under conditions closer to how the treatment might be used in actual practice. Few

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studies have directly compared these different sources of variation with respect to a single disease and treatment. Among asthma patients, over 60% of patients using inhaled corticosteroids (ICS) and long-acting ß-agonists (LABA) are managed with ICS and LABA products that are not fixed-dosed in a single inhaler, although the same branded product with the same medications and doses are marketed in both fixed-dose and multiple inhaler forms (W. Mapel & H. Roberts, 2014). Comparative effectiveness research (CER) describes several aspects of interest including research design, desired outcomes, and analysis techniques. One critical aspect of CER is to create a very precise definition of all of the parameters involved in the research discipline that could potentially impact the results. A rich description of the data includes an analysis of how any variation across these parameters impacts the findings of the CER studies. It is critical for this research to be completely reproducible. Since CER is a type of research that is likely to be conducted by others, and since much of the value of CER is in conducting multiple studies as a means to more efficiently learn, it is important that additional studies be conducted that are equivalent and this is only possibly if all of the underlying randomizations and choices are fully described.

13. Inhaled Corticosteroids in Children

Inhaled corticosteroids (ICS) became the standard of care for asthma in children in 1991 when a two-year study in schoolchildren with mild to moderate asthma first demonstrated that there was overall asthma control superior to bronchodilator treatment alone (M. C. van Aalderen & B. Sprikkelman, 2010). Chronic treatment with budesonide was far superior to treatment with the short-acting β2 adrenergic drug, salbutamol, with respect to asthma symptoms, lung function, and frequency of exacerbations. Optimal asthma control was not achieved at the same concentrations of inhaled steroid therapy; subjects with moderate-to-severe asthma symptoms required approximately three times the dose of inhaled flunisolide to achieve the same clinical efficacy in management of asthma symptoms as subjects with mild disease. These studies provide a solid foundation for our understanding of ICS and their role in paediatric asthma treatment. More recent studies largely confirm the findings of these early studies, while research over the last few years also considered long-acting beta agonists (LABA), leukotriene-modifying drugs, and newer ICS molecules in children. Despite the introduction of other medications for asthma, ICSs continue to be the recommended first-line maintenance therapy for paediatric asthma patients in numerous guidelines. However, different inhaled drugs may have differing effects of lung growth. A common concern is whether ICS leaves children shorter than their non-steroid treated peers. Height and lung function were therefore monitored in children included in long-term clinical trials during which beclomethasone and nedocromil were compared. Overall, mean increase in height was small but clinically insignificant. There was no evidence of

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carryover effect after cessation of ICS therapy. These results suggest that there is no need for concern about long-term effects of ICS therapy on height. Prospective trials are also required in order to further assess the effect of ICS on lung growth. Gaining a better understanding of how the lungs grow normally is important. A logical extension of these observations regarding normal lung growth is to ask what influence chronic rather than frequently administered drugs, namely, corticosteroids, may have on this complex process. Given the widespread use of these drugs in conditions such as asthma, it is pertinent that possible effects on normal lung growth are determined.

14. Safety During Pregnancy

Recent research has suggested that the regular use of inhaled corticosteroids is associated with a decrease in the birth weight of babies born to asthmatic mothers. It is recommended that the regular use of inhaled corticosteroids should not differ from guidelines during pregnancy in order to minimize the risk to mothers and babies. However, these studies have not taken asthma control into account. It was hypothesized that the regular use of inhaled corticosteroids will be associated with a decrease in the birth weight of the baby from poorly controlled asthmatic mothers, but not those with well control asthma. Methods: Data were used for singleton live births in Washington State between 2003 and 2007. Maternal medication use and fill data for the time periods before and during pregnancy were linked to children born to mothers with asthma. Asthma control was measured with a risk of asthma-related hospitalizations, emergency department visits, and oral corticosteroid use as a proxy. Results: The use of inhaled corticosteroids was not associated with a decreased birth weight for children born to mothers with either well or poorly controlled asthma. However, the results might be limited by the outcome of the crude asthma control measure used in the analysis. A written action plan should be offered, advice on continuing use of preventer be given. The regular use of inhaled corticosteroids (ICS) is an important part of asthma management, in particular to prevent exacerbations. A well recognized association between asthma severity symptoms, lung function and worse perinatal outcomes, including low birth weight and small-for-gestational-age infants (E. Murphy, 2015).

15. Interactions with Other Medications

Inhaled corticosteroids may interact with other medications. Because these drugs act on many organs, there is the potential for serious interactions with many different drugs. The objective of this article is to review the potential for such interactions. Reviewed studies and case reports related to inhaled corticosteroid interactions and their mechanisms are summarized. When corticosteroids pass through the liver, they are metabolized by cytochrome P450 (CYP) 3A4.

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Therefore, drugs metabolized by CYP3A4, such as macrolides, human immunodeficiency virus (HIV) protease inhibitors, and drugs with a high absorption rate, are prone to interactions with inhaled corticosteroids.

Fluctuation of the plasma concentration of the corticosteroid component of inhaled corticosteroids may induce an endocrinological response that would normally be suppressed. It is the main purpose of understanding the magnitude and mechanism of drug-drug interaction to select an appropriate countermeasure. Manufacturers of inhaled corticosteroids should provide such information to securely use these products. Inhaled corticosteroids are important drugs in the treatment of patients with asthma and chronic obstructive pulmonary disease. Along with beta2-agonists, a bronchodilator, multiple inhalation drugs have appeared in a plastic case. Interaction with other drugs is unavoidable if two or more drugs are administered via the same organ (Latorre et al., 2015).

16. Emergency Management of Asthma Exacerbations

You've learned well. You know that severe acute exacerbations of asthma can be fatal. Any time you get out of breath, use a bronchodilator inhaler. If it doesn't fix the problem quickly, start oral corticosteroids. If the situation still doesn't improve fast, call emergency services. Once these steps are taken, lastly check an LD peak flow and go to hospital if it is under 50%. You well remember that time when, years ago, you had that barnyard cough for a month. You should have known better. Oral steroids should have been enough to bring the inflammation under control. Why didn't you seek further medical advice when it became clear after two weeks the oral steroids were not sufficiently helping or after three weeks when relief appeared to coincide with ceasing exercise? If you had attended a follow-up appointment within 4 weeks, then continuing symptoms could have been revealed, allowing additional treatment (either a higher dose of oral corticosteroids or the addition of a long-acting bronchodilator to the inhaled corticosteroids). Chronic cough tolerances aside, you had a peak flow diary, which once shows readings <60% predicted, is a RED FLAG. Additionally, other possible causes of symptoms, such as pulmonary embolism, should have been investigated. Only some serious re-evaluation concerning patient management would allow sending someone with an acute exacerbation from an oral corticosteroid-dependent severe asthma in the past patient category home with a mere 5-day course of oral corticosteroids without a script for a further 5-day course of oral corticosteroids or alternative instructions for escalating the inhaled corticosteroids dose in a form other than a written action plan were discussed. And the inhalers! It is ALWAYS standard practice to check a patient's inhaler technique during acute exacerbation management. Poor technique can negate the effects of inhaled corticosteroids and reliever (disproportionately the inhaled corticosteroids).

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Dropout could result with certain inhibitors. Ensure the pMDI has not expired as this information is not shown on the canister but only on the packaging. Last, check the dose counter on the pMDI so as to not use an empty one.

17. Patient Case Studies

Case Study 1

Maritza is a 25-year-old Hispanic female who has asthma and recently sought care with her primary care provider. She reports increased use of her albuterol inhaler to at least five to six times per day. The primary care provider prescribes Maritza an inhaled corticosteroid medication. Maritza is hesitant to use this medication and wonders why her oral prednisone was decreased if this medication is considered a steroid. What patient education should the provider include in support of promoting adherence to this inhaled corticosteroid medication for Maritza?

Pharmacologic treatment of asthma is divided into two categories of treatment including quick-relief medications and long-term control medications. Quick relief medications consist of short-acting beta-agonists (SABA), Ipratropium bromide, and oral corticosteroids. Long-term control medications consist of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), leukotriene inhibitors, and Theophylline. Albuterol is a short-acting beta-agonist medication that is most beneficial for quick relief. If ICS therapy is used to maintain asthma control, patients with asthma prove to have less quick-relief medication use of albuterol. Prednisone is an oral corticosteroid medication used to reduce airway inflammation in the absence of inhaled corticosteroids. Maritza should be encouraged to use the prescribed inhaled corticosteroid medication. Inhaled corticosteroids are preferred in the treatment of asthma because they deliver the medication directly to the airways. Maritza should be taught to rinse her mouth with water after she uses the ICS medication to reduce the risk of oral candidiasis infections. Inhaled corticosteroids take several weeks to provide a beneficial effect in reducing airway inflammation. She should be prescribed a 4-week follow-up appointment to reassess asthma control and medication use.

Case Study 2

Emmett is a 15-year-old Caucasian male who has been using a combination albuterol/ipratropium inhaler 3–4 times a day. His provider considers starting Emmett on an inhaled corticosteroid and discusses the potential for supporting Emmett's overall lung health and preventing asthma attacks. Emmett reports he is concerned about the potential weight gain

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which he heard could result from inhaled corticosteroids. What patient education should be provided to Emmett regarding adherence to inhaled corticosteroid medication?

18. Future Directions in Asthma Treatment

Imagining the future of a disease after the ground covered by thousands of investigators throughout the world is a real challenge—especially on a worldwide scale, for a human disease as fascinating and complex as asthma. Efforts must be combined from clinicians (including from primary care and emergency departments), from researchers (mostly bench researchers, basic immunologists, cellular and animal researchers), asking the pertinent questions, with patients playing probably now the most important part to deal with the communication between the three first-mentioned worlds and to speed up the relevant trials and improvements, and finally from industry to transform the relevant results in groundbreaking therapeutic advances. Science and wisdom should thereby not be invoked for a purpose that eludes their commencement, but, and necessarily, in exordium (Charriot et al., 2016). The odd aspect of things primarily considered gives birth to innumerable realizations that follow, so the therapeutic management of asthma is paramount and relevant from the outset.

Asthma as the Wild Territory is an editorial dedicated to the future treatment of asthma. More than 150,000 publications matching the keyword “asthma” were retrieved by the search engine PubMed. Moreover, during the process, thumbnails were read from a manual search, video works were observed, and some congresses, symposia, colloquiums were attended. There is little formal doubt that the vast majority of information was updated and correctly absorbed, but a personal ground gives rise to creative or realized hopes; to get out of a stoic propriety, the adumbration of new thinking is only well-founded (Lommatzsch & Stoll, 2016).

19. Conclusion

When combined with a long-acting beta-agonist (LABA), ICS is considered a recommended treatment option for a majority of patients with mild persistent asthma, as well as patients with moderate to severe asthma. In most clinical trials of ICS, ICS are administered in the 200-800 μg per day dose range. ICS are lipophilic and have high first-pass metabolism. This makes them available to the lung by inhalation administration and causes acute administration of a very high dose to be metabolized at a high first-pass rate (Daley-Yates et al., 2023). One of the common observations in patients with asthma is that over a period of several years, there is a slow deterioration in asthma control leading to the presentation of more severe symptoms. This deterioration is believed to be caused by a continuous increase in the level of airway inflammation and other changes (airway remodeling). The inflammation can be monitored by

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profiling airway and alveolar washings or by using the sputum-induced technique. At this time, there is no published large clinical study correlating the effect of changing ICS effects on long-term FEV1 with the usefulness of asthma control and anti-inflammatory effects.

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