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SAFETY, EFFICACY AND MANAGEMENT OF ASTHMAWITH ICS/LABA THERAPY: A REVIEW

Kavya Catherin*, Jelany K. Raju, Lal Jose E., Happy Thomas and Rosmin Jacob

Department of Pharmacy Practice, St. James College of Pharmaceutical Sciences, Chalakudy, Kerala.

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***Corresponding Author**
Kavya Catherin
Department of Pharmacy Practice, St. James College of Pharmaceutical Sciences, Chalakudy, Kerala.

ABSTRACT

Asthma is a chronic inflammatory condition of the airways. Management of asthma with Inhaled Corticosteroids (ICS) and Long acting β2 agonist (LABA) in patients with persistent symptoms or uncontrolled asthma with a low to moderate dose of ICS alone, improves asthma control, decrease the exacerbation and future risks. Commonly prescribed ICS/LABA therapy includes, Salmeterol/ Fluticasone, Fluticasone/ Formoterol, Budesonide/ Formoterol. Various studies conducted have demonstrated the efficacy and potency of different ICS/LABA combination therapy. However, the uses of these medications have raised safety concern also. The purpose of this review is to establish the safety, efficacy and management of ICS/ LABA therapy from various reviews and studies conducted.

KEYWORDS: Asthma, ICS, LABA, safety, efficacy, treatment, SABA, side effects.

INTRODUCTION

Asthma is a chronic inflammatory disease of airways which is characterized by recurrent attacks of breathlessness and wheezing with airway hyper-responsiveness to various triggers such as tobacco smoke, air, allergens, pollen, dust etc.

Treatment with inhaled corticosteroids (ICS) and Long Acting β2 Agonist (LABA) either separately or as a fixed dose formulation, is recommended for patients, where asthma is not controlled adequately. Many different ICS/LABA fixed dose combinations are available like Budesonide/Formoterol, Salmeterol/Fluticasone propionate, Beclomethasone/Formoterol, Fluticasone/Formoterol etc. with their efficacy in patients demonstrated in several large scale

randomized trials.

Addition of LABA like Formoterol and Salmeterol to maintenance treatment with ICS improves asthma control and are found to have more beneficial effects than the addictive effects of theophylline and anti-leukotrienes.

Pathophysiology

Asthma is mediated by immunoglobulin E (IgE) and precipitated by an allergic response to an allergen such as pollen or animal dander. Sensitization occurs at first exposure, which produces allergen-specific IgE antibodies that attach to the surface of the mast cells. Upon subsequent exposure, the allergen binds to the allergen specific IgE antibodies present on the surface of the mast cells, which leads to the release of inflammatory mediators such as leukotrienes, histamines and prostaglandins. These inflammatory mediators cause bronchospasm which triggers an asthma attack.

If an asthma attack is left untreated, eosinophils, T helper cells and mast cells migrate into the airways. Excess mucus production caused by goblet cells plug the airway and leads to increased airway tone hyper-responsiveness.

Management

- LABA trials show increase in asthma deaths of 1 death in 1000 patient-years of use but this risk is less when used with ICS.
- When low dose inhaled steroids fails to control asthma symptoms, long acting β2agonist can be added or increase dose of steroids.
- Combination of ICS/LABA inhalers improve adherence when compared to separate inhalers.
- Different ICS/LABA combinations for asthma are Budesonide/ Formoterol, Salmeterol/ Fluticasone, Beclomethasone/ Formoterol, Fluticasone/ Formoterol and Vilanterol/ Fluticasone furoate.

Mechanism

Corticosteroids

Corticosteroids bind to the Glucocorticoid receptor (GR) present in cytoplasm. Activated GR translocates to nucleus to exert its effects. Activated GR binds with Glucocorticoid Responsive Elements (GRE) to induce the formation of anti-inflammatory mediators

(transactivation) and inhibits transcription factors AP-1 and NK-KB which results in a decreased production of pro-inflammatory mediators (transrepression).

β2 agonists

β2 agonists bind to β2 receptors on airway smooth muscle,increase cyclic AMP which results in airway smooth muscle relaxation and produce bronchodilation and anti-inflammatory effects.

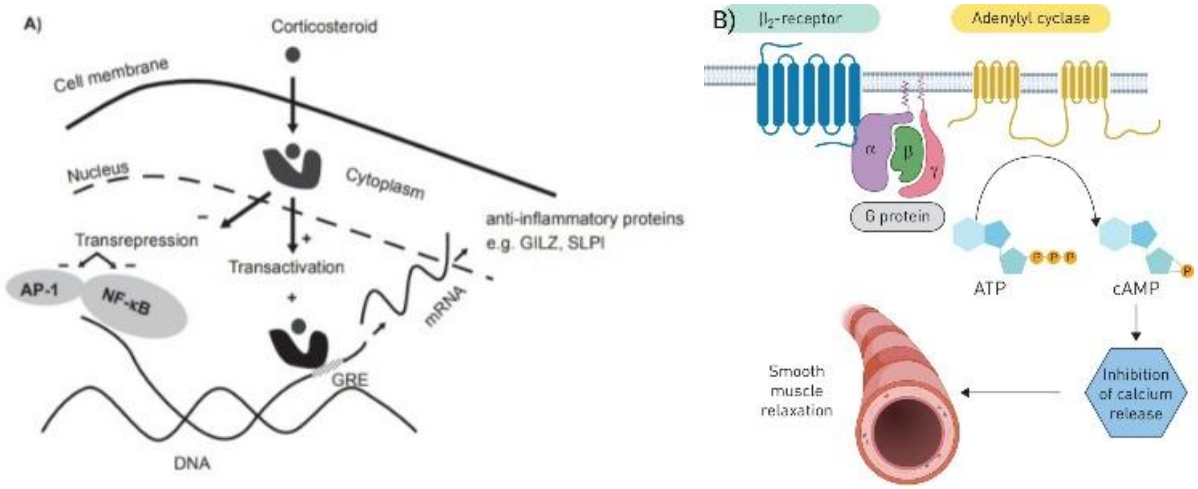

Fig. 1: A) Mechanism of action of Corticosteroids, B) Mechanism of action of β2 agonist.

Interaction between β2 agonists and ICS

Effect of β2 -receptor agonist on corticosteroids

- β2 agonists potentiate the anti-inflammatory effect of corticosteroids and increase the expression of GR and also enhance the translocation of GR from the cytoplasm into the nucleus.
- Studies shown that inhalation of both Fluticasone (500 µg) and Salmeterol (50µg) induced translocation of GR from the cytoplasm to the nucleus.
- The addition of Formoterol increase the effect of Budesonide to inhibit proliferation of human airway smooth muscle cells through activation of cell cycle control protein p21.

Effects of corticosteroids on β2 receptor

- Corticosteroids prevent desensitization at various levels and increases β2 receptor transcription. Intranasal Beclomethasone 100 µg twice daily for 3 days increases β2 receptor expression.

Pharmacology of LABAs: Difference between Formoterol and Salmeterol

- Formoterol and Salmeterol are more lipophilic than SABA, therefore larger proportion will rapidly diffuse through the airway and has a higher pharmacological efficacy than Salmeterol.
- In addition, the effects of Formoterol were dose dependent and Salmeterol did not showa clear effect at doses higher than 50 µg.

Combination of ICS and LABA in the treatment of asthma patients

- In patients whose asthma is not well controlled, with low dose of ICS, then increase the dose of ICS or add a LABA to improve control.
- Addition of Formoterol to Budesonide shown enhanced control, higher number of episode free days, greater improvements in day and night time symptom scores.
- Studies showed that patients with uncontrolled asthma receiving a low dose ICS had little improvement and if Salmeterol (50 µg bid) was added to same dose of Beclomethasone shown greater improvements.

Dose response relationship

ICS and LABA therapy has shown efficacy in adolescent and adult asthma patients when prescribed according to 3 regimens that is; a fixed maintenance dose ICS/LABA along with SABA for relief, as an ICS/fast onset LABA for maintenance and as reliever therapy. The study conducted by Richard Beasley et al in 2019 aimed to evaluate from published randomized controlled trials (RCTs), to compare the dose response relationship of combination ICS/fast onset LABA when used either as reliever therapy or regular maintenance therapy. The study included 2 design that is; Study design 1, which was done to find out the potency evaluation-Budesonide/Formoterol reliever monotherapy versus Budesonide/Formoterol fixed dose maintenance. Study design 2, was done to determine the efficacy evaluation of Budesonide/Formoterol maintenance and reliever therapy versus higher fixed dose Budesonide/Formoterol maintenance therapy.

From the limited evidence available it was reported that the difference for potency was substantial with an estimated 46 fold difference with Budesonide /Formoterol reliever monotherapy compared with Budesonide/Formoterol fixed maintenance therapy. There was an additional 26% reduction in severe exacerbation risk with Budesonide/Formoterol reliever therapy compared with higher fixed dose maintenance therapy & SABA reliever therapy. The

Budesonide/Formoterol maintenance and reliever group had a decreased risk of severe exacerbation compared with the other therapy. The calculated dose ratio for ICS/LABA administration was 0.75.

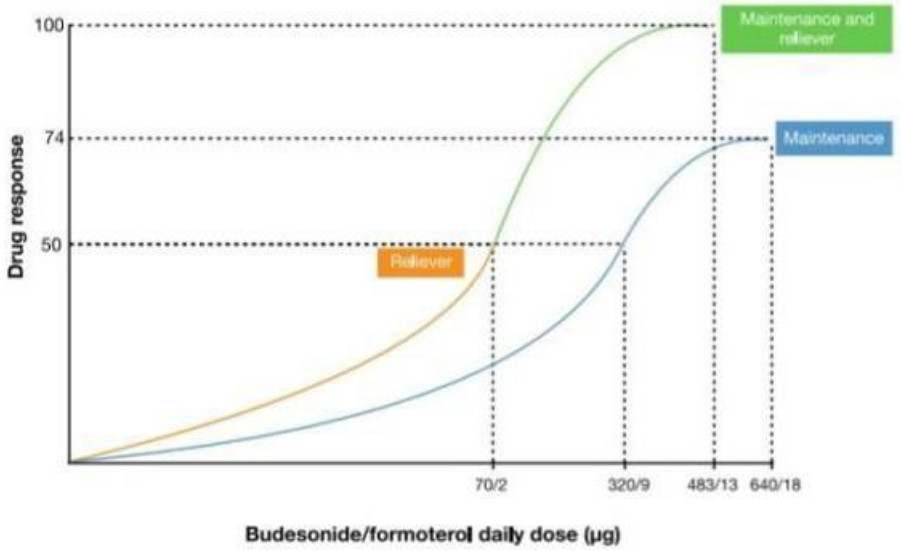

Fig. 2: Schematic dose response curve of severe exacerbation risk for budesonide/formoterol reliever therapy and maintenance budesonide/ formoterol therapy.

The study concluded that Budesonide/Formoterol reliever therapy has greater potency and efficacy than regular maintenance Budesonide/Formoterol plus SABA reliever therapy in reducing the risk of severe exacerbation.

Safety and Efficacy

The efficacy assessments was done by measuring the mean change in FEV_1 and safety assessment were carried out throughout the study based on adverse events reported, vital sign, a 12 lead ECG and clinical laboratory testing. Fluticasone/Formoterol combination therapy demonstrated a good safety profile and well tolerated during the 12 week treatment period.

Another study conducted, compared PEF (Peak Expiratory Flow) as a primary variable between a group administered 400 µg/day BDP (Beclomethasone diproprionate) plus 100µg/day Salmeterol and a group administered 1000µg/day BDP alone for 6 months in mild to moderate asthma. The add-on therapy with Salmeterol resulted more favorable outcome in terms of PEF. Recent multicenter, randomized double-blind studies showed that treatment with Budesonide/Formoterol & Fluticasone /Salmeterol were associated with lower risk of

asthma exacerbation than alone therapy.

Side effects

Local side effects

Oral candidiasis, cough at time of inhalation, hoarse voice are found to be some local side effects. Cough is due to local irritants and can be resolved by using spacer chamber or slow rate inhalation.

Systemic side effects

Systemic side effects of ICS depends on various factors like delivering device used, dose, site of delivery and also it varies among individuals . A spacer reduces oropharyngeal deposition and increases delivery of drug to the lungs and helps to reduce systemic absorption.

Hypothalamus-Pituitary-Adrenal(HPA) Axis suppression

The most serious adverse effect of ICS is dose related suppression of the HPA axis. In adults, HPA suppression appears to occur at doses above 800µg/day BDP equivalent. It is alsofound that even low to medium ICS dose can disturb basal cortisol secretion in children and adult.

Infections & Pneumonia

Increased risk of pneumonia in COPD or asthmatic patients on ICS therapy. A dose response relationship was present with higher ICS dose, and associated risk of pneumonia. The risk was found to be more with fluticasone than that seen with Budesonide.

Skin Thinning and Bruising

Patients receiving high dose ICS is found to have side effects like skin bruising and thinning. Oral thrush, muscle cramps, muscle twisting, hand tremor and heart palpitation are the other side effects.

CONCLUSION

The commonly used ICS/LABA therapy for asthma includes Budesonide/Formoterol, Salmeterol/Fluticasone and Fluticasone/Formoterol .The collected data demonstrates the positive impact of ICS /LABA therapy on lung function, airway hyper-responsiveness, reduction in severe exacerbation and improved asthma outcome. Various studies conducted reported that ICS/LABA therapy are efficacious and well tolerated treatment for asthma and reduced future risk in patients. Side effects of the therapy includes oral candidiasis, cough, hoarseness, HPA axis suppression, skin thinning, bruising, muscle cramps etc.

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