The Pharmaceutical and Chemical Journal, 2025, 12(2):89-94

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Budesonide and Formoterol Fumaroate: A Review of Their Use in Combination Therapy for Respiratory Disease (COPD & Asthma)

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Abstract: Asthma and chronic obstructive pulmonary disease (COPD) are prevalent, chronic respiratory diseases characterized by airflow obstruction and inflammation. Despite their distinct pathophysiology, an overlap syndrome often occurs, particularly in older patients, displaying features of both conditions. Budesonide and formoterol fumarate, when used in combination therapy, have shown efficacy in managing these conditions. Budesonide, a potent glucocorticosteroid, works by reducing inflammation, while formoterol, a long-acting β2-adrenergic agonist, provides sustained bronchodilation. In combination, they offer improved lung function, reduced exacerbations, and enhanced quality of life in COPD and asthma patients. This review discusses the pharmacological properties and clinical outcomes of budesonide/formoterol combination therapy, focusing on its role in patients with overlapping asthma and COPD. Studies demonstrate that this combination is well tolerated and effective, particularly for patients inadequately controlled with standard therapies.

Keywords: Asthma and chronic obstructive pulmonary disease, COPD, Respiratory Disease

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are long-term respiratory conditions that involve varying levels of airflow restriction, inflammation, and tissue damage (1). Asthma, often triggered by allergies and usually developing in childhood, is marked by reversible airflow obstruction. It tends to follow an episodic course and generally has a positive prognosis due to its good response to anti-inflammatory treatments. On the other hand, COPD is primarily linked to tobacco use, typically emerging in middle age or later, and is characterized by a partially irreversible airflow limitation. This leads to a progressive decline in lung function and often results in premature death (2,3). While these definitions emphasize the physiological and structural distinctions between asthma and COPD, in clinical practice, many older individuals display characteristics of both diseases, prompting a reconsideration of the view that asthma and COPD are separate conditions. Both are chronic inflammatory lung diseases, and the inflammation in each is associated with structural alterations in the airways, both large and small. This overlap can result in a combined syndrome that exhibits features of both asthma and COPD (4,5).

What is the Overlap Between Asthma and COPD?

An overlap syndrome occurs when a patient exhibits features of more than one condition. The overlap between asthma and chronic obstructive pulmonary disease (COPD) may arise due to inflammatory or immune mechanisms, as well as structural changes in the airways (6). Recognizing this overlap requires assessing both increased variability in airflow and incompletely reversible airflow obstruction. Several studies have shown that partial

reversibility is present in patients with obstructive airway diseases, both in the short and long term (7,8). Identifying the presence of hyperresponsiveness may help differentiate between the two conditions and provide insights into their development and progression (9).

Recent research has revealed that 17% to 19% of patients with obstructive airway diseases have characteristics of both asthma and COPD, confirming that overlap is common, particularly in older individuals. Objective testing has highlighted the overlap in this population, making it an increasingly important clinical consideration (10,11).

The inflammatory profiles of asthma and COPD may sometimes overlap, complicating their distinction. Typically, asthma is characterized by an inflammatory response rich in CD4+ lymphocytes, eosinophils, and macrophages (12,13). In contrast, COPD is marked by an increase in CD8+ T cells, neutrophils, and macrophages in the bronchioles and alveoli. However, severe asthmatics or those who smoke often show higher numbers of neutrophils, especially in bronchoalveolar lavage fluid and biopsies, which is more typical of COPD. Moreover, in COPD patients, particularly those experiencing acute exacerbations, tissue eosinophilia is often present and correlates with a favorable response to steroid therapy (14,15).

Asthma is predominantly driven by Th2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13, and upregulation of chemokines like RANTES, eotaxins, and monocyte chemoattractant protein-1. On the other hand, COPD is characterized by Th1-dominated responses, with an increase in interferon-γ production by CD8+ T cells (16). Key inflammatory mediators in COPD include neutrophil chemokines like IL-8, leukotriene B4, IL-1, and tumor necrosis factor-α (TNF-α). Interestingly, some COPD patients, particularly during exacerbations, exhibit higher levels of TNF-α, which may indicate asthma-like inflammation, with the production of allergic mediators such as IL-4, IL-5, and IL-13(17,18).

Current guidelines suggest that some patients with asthma may have a fixed or irreversible component of airway obstruction, further blurring the lines between asthma and COPD. Recognizing phenotypic characteristics, such as symptoms, allergy status, and bronchodilator response, is critical in understanding and managing these overlapping conditions.

2. Pharmacology and Pharmacodynamics of Budesonide

Budesonide is a nonhalogenated corticosteroid with strong glucocorticoid and weak mineralocorticoid activity. It binds to glucocorticoid receptors in most cells, inhibiting immune cells like lymphocytes, eosinophils, and mast cells. Budesonide also targets inflammatory mediators such as cytokines and leukotrienes (19,20). Additionally, it boosts anti-inflammatory proteins like lipocortin-1 and IL-10, while increasing β2-adrenergic receptor expression. These actions help make budesonide effective in treating asthma and other inflammatory conditions (21,22).

Budesonide: Molecular Mechanisms of Action

Like all glucocorticoids, budesonide is a lipophilic molecule that easily crosses cell membranes to bind with the cytoplasmic glucocorticoid receptor (GR). The GR exists predominantly as the GRα isoform, with a less common, non-functional GRβ isoform (22,23). Budesonide has a high binding affinity for this receptor. When compared to dexamethasone (which is assigned a reference value of 100), budesonide exhibits a relative GR affinity of 935 (24).

3. Pharmacology and Pharmacodynamics of Formoterol

Formoterol is a selective long-acting β2-adrenergic receptor agonist (LABA) that delivers a significant and lasting bronchodilatory effect for up to 12 hours after a single dose. Its onset of action is notably faster than that of salmeterol, another LABA, although both have similar durations of effect. When it comes to improving lung function and controlling symptoms of chronic obstructive pulmonary disease (COPD), formoterol's efficacy is comparable to salmeterol and may even surpass that of ipratropium or theophylline. Furthermore, formoterol offers added benefits when used in combination with other bronchodilators or inhaled corticosteroids. Clinical trials show that formoterol is generally well tolerated, with an adverse event profile similar to other β2-adrenergic receptor agonists. As a fast-acting, well-tolerated, and effective option, formoterol is an ideal long-acting bronchodilator for patients with moderate to severe COPD (25,26).

Formoterol Molecular Mechanism

Formoterol is a relatively selective long-acting beta2-adrenergic receptor agonist, though it does exhibit some activity at beta1 and beta3 receptors as well. Beta2 receptors are primarily located in bronchial smooth muscle, with a smaller presence in cardiac tissue, while beta1 receptors are mainly found in the heart. This selectivity for beta2 receptors is particularly beneficial in treating pulmonary conditions like COPD and asthma. Formoterol has been shown to have about 200 times greater affinity for beta2 receptors compared to beta1 receptors (27,28).

At the molecular level, when formoterol activates beta receptors, it stimulates the enzyme adenylyl cyclase, which converts ATP into cyclic AMP (cAMP) (29). The increased cAMP levels in bronchial smooth muscle tissue lead to muscle relaxation and airway dilation. Additionally, this process helps inhibit the release of hypersensitivity mediators, such as histamine and leukotrienes, from cells like mast cells (30).

Budesonide and formoterol in combination

Budesonide/formoterol is an inhaled fixed-dose combination therapy that includes the inhaled corticosteroid (ICS) budesonide and the long-acting muscarinic antagonist (LAMA) glycopyrronium, along with formoterol fumarate. It is approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD). In two pivotal phase III trials lasting 24 to 52 weeks, budesonide/formoterol was shown to reduce the rates of moderate and severe COPD exacerbations and improve lung function more effectively than budesonide/formoterol alone or formoterol alone. Additionally, it demonstrated beneficial effects on symptoms like dyspnoea, reduced the need for rescue medications, and improved health-related quality of life (HR-QOL). Budesonide/formoterol also lowered the risk of all-cause mortality. The combination therapy was generally well tolerated, with a safety profile similar to that of its individual components. Budesonide/formoterol offers a convenient and effective maintenance treatment option for COPD patients, including those whose condition is not adequately controlled with dual ICS/LABA or LAMA/LABA therapies.

Pharmacodynamic Budesonide and formoterol in combination

The pharmacological properties of budesonide and formoterol are well established. This section primarily focuses on the pharmacological profile of budesonide/formoterol, a fixed-dose combination (FDC) of two bronchodilators with distinct mechanisms of action and a glucocorticosteroid, delivered via a co-suspension technology (31). Budesonide is a potent glucocorticosteroid with a rapid onset and dose-dependent anti-inflammatory effects in the airways. Formoterol, a selective long-acting beta2-adrenergic agonist (LABA), acts quickly (within 1–3 minutes after inhalation) and provides sustained bronchodilation for over 12 hours following a single dose. It demonstrates a higher binding affinity for β2- over β1-adrenoreceptors, leading to rapid bronchial smooth muscle relaxation in patients with reversible airway obstruction, with the bronchodilator effect being dose-dependent (32,33).

Budesonide/formoterol, when delivered via a pressurized metered-dose inhaler (pMDI), utilizes co-suspension delivery technology. This technology creates a uniform mixture of drug crystals and porous phospholipid particles, allowing for the simultaneous delivery of multiple drugs from one inhaler. The technology ensures excellent dose consistency, stability, and minimizes the potential for drug-drug interactions in combination therapies(34). Studies have demonstrated the reliability, robustness, and consistency of the co-suspension delivery system used in the budesonide/formoterol pMDI. In patients with moderate to severe COPD, radiolabelled budesonide/formoterol was efficiently deposited in both central and peripheral lung regions, with 32.1% of the emitted dose detected in the lungs (35). The radiolabelled dose showed uniform deposition across the lungs regardless of disease severity (36).

Due to the potential for additive pharmacodynamic effects and class-related adverse reactions, concomitant use of budesonide/glycopyrronium/formoterol with other LAMA- or LABA-containing products is not recommended (37).

Lung Function Budesonide and formoterol in combination

In the spirometry sub-study of the ETHOS trial, budesonide/formoterol significantly improved FEV1 AUC 0–4 compared to both budesonide/formoterol alone and morning pre-dose trough FEV1 responses (38). It also showed nominally significant improvements in FEV1 AUC 0–4 and morning pre-dose trough FEV1 compared to formoterol alone, both over 24 weeks and at week 24. These improvements in lung function with budesonide/formoterol were sustained throughout the 52 weeks of treatment (39,40). In conclusion, budesonide/formoterol is effective and generally well tolerated in patients with moderate to very severe COPD. It offers a valuable and convenient option

for the maintenance treatment of COPD, particularly for those whose condition remains inadequately controlled with dual ICS/LABA or LAMA/LABA therapies.

4. Conclusion

Budesonide/formoterol combination therapy is a highly effective and well-tolerated treatment for asthma and COPD, including patients with overlap syndrome. The combination of budesonide, a corticosteroid, and formoterol, a long-acting β2-agonist, offers synergistic benefits, improving lung function, reducing exacerbations, and enhancing quality of life. This therapy also shows promise in patients whose conditions remain inadequately controlled with traditional dual therapies. Overall, budesonide/formoterol provides a convenient, reliable option for the maintenance treatment of respiratory diseases, particularly for those with both asthma and COPD characteristics, and offers a significant advancement in managing these complex and overlapping conditions.

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