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Retraction

Retracted: Biochemical Behaviours of Salmeterol/Fluticasone Propionate in Treating Asthma and Chronic Obstructive Pulmonary Diseases (COPD)

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] H. Mills, R. Acquah, N. Tang et al., "Biochemical Behaviours of Salmeterol/Fluticasone Propionate in Treating Asthma and Chronic Obstructive Pulmonary Diseases (COPD)," *Emergency Medicine International*, vol. 2022, Article ID 2593740, 5 pages, 2022.

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Review Article

Biochemical Behaviours of Salmeterol/Fluticasone Propionate in Treating Asthma and Chronic Obstructive Pulmonary Diseases (COPD)

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Chronic obstructive pulmonary diseases (COPD) and asthma are fatal. The respiratory tract may be blocked, robbed of the adequate amounts of oxygen; hence, death ensues if a quick medical attention is not provided. The treatment available for the duo are inhaled corticosteroids (ICS). The ICS can work synergically with LABAS (long-acting β_2-antagonists) and so many other medicines like bronchodilators. The drugs used for the treatment of asthma and COPD are metabolised once in the body system and at the same time exerting the therapeutic effect provided the concentration of the drug is within the therapeutic window. The CYP3A isoforms metabolise the ICS, in this case, salmeterol and fluticasone propionate (FP). Methods of administration are not limited to inhalation. Specific doses are prescribed accurately paying attention to factors like age, gender, race, and genetic makeup since these affect drug metabolisms. Generally, the ICS work by translocating glucocorticoid receptors to the nucleus from the cytosol. The mechanism is potentiated by the β-antagonists and this brings about an anti-inflammatory effect which is greater than either of the two drugs alone. Once this happens, it is not necessary to increase ICS dose. The ICS, in addition, cause more production of β-receptors by activating the β-receptor genes. This mode of action begets the LABAs' bronchodilator-effects. The challenge is that ICS are not limited only to "double" therapy. Analysing such therapies is daunting since coadministration interferes with pharmacology and pharmacokinetics of drugs. This work focuses on salmeterol/fluticasone propionate combination and aspects which has to do with administration, monitoring, metabolism, toxicity, and adverse effects.

1. Introduction

Patients who suffer from chronic obstructive pulmonary diseases (COPD) are mainly treated with inhaled corticosteroids (ICS). The medicine is normally administered to COPD patients who are known to have a history of exacerbation. Reports say that the ICS treatment alone could not restore or improve the pulmonary function in COPD individuals. Howbeit, the ICS monotherapy mitigated COPD exacerbation and revealed symptom improvements. The COPD patients, as a result, are treated with ICS in combination with other drugs like long-acting β_2-antagonists (LABAs). It is reported that the combination treatment (ICS-LABAs) improved lung functionality, health status, and minimised COPD severity. Therefore, the combination treatment is highly recommended specifically for the patients with exacerbation history regardless of the long-acting bronchodilators monotherapy [1].

The ICS therapy is of great effect to individuals suffering from bronchial inflammation. The diagnosis of the bronchial inflammation is done by determining eosinophil levels in the blood. High levels of eosinophils are a compass that points to the inflammation of the bronchioles. Apart from high eosinophil blood levels, asthma history, and COPD-asthma overlap are also pointers to bronchial inflammation. Occasionally, ICS use has a downside of increasing the risk of pneumonia. Not all of the ICS are known for the aforementioned disadvantage but some specific ones [1].

2. COPD and History of ICS Use

A group of diseases that causes limitation to airflow thus giving rise to some progressive respiratory symptoms are collectively known as chronic obstructive pulmonary diseases (COPD). The management of COPD is daunting mainly because the pathophysiology of the diseases is not well known. Individuals who smoke and those who inhale dangerous particles are subject to inflammatory changes [2]. Some studies conducted in the 1990s on ICS monotherapy for individuals suffering from chronic bronchitis and COPD revealed that anti-inflammatory drugs mitigated inflammation of the bronchioles. The same anti-inflammatory agents showed a variation in lung-function parameters like peak expiratory flow (PEF) and forced expiratory volume (FEV) [3].

It was observed that synergism works perfectly. Consequently, drugs that work via different mechanisms are favourable in achieving synergism. The combination of LABAs and ICS is one of the common combination treatments for COPD [4]. The ICS work by translocating glucocorticoid receptors to the nucleus from the cytosol. The mechanism is potentiated by the β-antagonists and this brings about an anti-inflammatory effect which is greater than either of the two drugs alone [5]. Once this happens, it is not necessary to increase ICS dose. The ICS, in addition, cause more production of β-receptors by activating the β-receptor genes. This mode of action begets the LABAs' bronchodilator-effects [1].

This article serves to highlight the treatment of COPD by salmeterol-fluticasone propionate combination, the metabolism of the drugs in the body, and the mode of action of the drug combination; amongst an endless list of possible treatments. Table 1 shows other possible drug combinations used to treat COPD and their pooled effect estimates (LABA on moderate-severe exacerbations).

3. Salmeterol

The drug salmeterol (Figure 1) is not only known for treating asthma but also COPD. It is an antagonistic β_2-adrenoceptor. It is reported that the salmeterol bronchodilatory effect can last for over 12 hours [7]. Acute asthmatic attacks cannot be subsided by salmeterol since it takes roughly 2 to 3 hours to reach its maximum levels in the blood following a single dose [8]. According to research conducted by Kirjavainen et al. [7]; salmeterol reached its maximum level (peak) 4 minutes following administration with a half-life of 11 hours.

The drug is metabolised mainly by the CYP3A4. The cytochrome P450 isoform, CYP3A4, oxidises the aliphatic base the drug. It is reported that salmeterol is severely metabolised via hydroxylation reactions forming α-hydroxy-salmeterol. The salmeterol-biotransformation products are then eliminated via urine (23%) and faeces (57.4%) [9]. Salmeterol systemic concentrations are undetectable at recommended doses.

Concomitant use of other drugs that metabolise CYP3A4 at low doses cannot cause clinically significant interaction [10]. However, caution should be exercised in patients with reduced clearance due to severe hepatic impairment. In addition, CYP34A inhibitors may exacerbate the cardiovascular and systemic side effects of corticosteroids. Dilation of the bronchi and increased airflow in the bronchioles [11, 12]. Although the mechanisms and doses of administration are different, studies have shown that all treatments and their effectiveness are comparable [13]. Paradoxical bronchospasm has been reported in patients using dose inhalers rather than dry powder inhalers [14].

Fluticasone-salmeterol powder for inhalation twice daily for the treatment of asthma in patients 12 years of age and older [15]. The initial dose is determined by the severity of the asthma. Instead, two inhalations of fluticasone/salmeterol 45/21, 115/21, 230/21 μg inhalations are administered twice a day. After inhalation, the patient should understand that in order to prevent oral candidiasis, rinse their mouth with water, and spit out the contents without swallowing [16]. The standard recommendation for the treatment of asthma in children aged 4 to 11 years is 100/50 μg of fluticasone/salmeterol as an inhalation twice a day [15]. The safety and efficacy of children under 4 years of age have not been established. For the sponsoring treatment of bronchospasm associated with chronic obstructive pulmonary disease, a single 250/50 μg inhalation twice daily is recommended approximately 12 hours apart [17].

The most common side effects with salmeterol in patients are with asthma (frequency ≥3%). The most common side effects in patients with chronic obstructive pulmonary disease are pneumonia, pharyngitis, respiratory viral infection, oral candidiasis, dysphonia, headache, and musculoskeletal disorders [18].

These symptoms include angina pectoris, tachycardia, hypertension, low blood pressure, arrhythmias, palpitations, and fatigue. These adverse pharmacological effects are mainly associated with peripheral vasodilation, hypoxemia, hypokalaemia, and reflex activation in response to direct stimulation of cardiac beta-adrenergic receptors [19]. Paradoxical bronchospasm, laryngeal spasm, and swelling of the throat may occur. Long-acting beta-agonists (LABAs) increase the risk of heart failure in people with COPD [20].

Table 1: Other possible drug combinations used to treat COPD and their pooled effect estimates (LABA on moderate-severe exacerbations) [6].

Combination.	Dosage, respectively	Hazard ratio at 95% credibility interval
Beclomethasone dipropionate/formoterol	200 μg/12 μg	0.96
Mometasone furoate/formoterol	200 μg/10 μg	0.68
Fluticasone propionate/salmeterol	500 μg/50 μg	0.81
Budesonide/formoterol	320 μg/9 μg	0.74
Fluticasone furoate/vilanterol	100 μg/25 μg	0.77

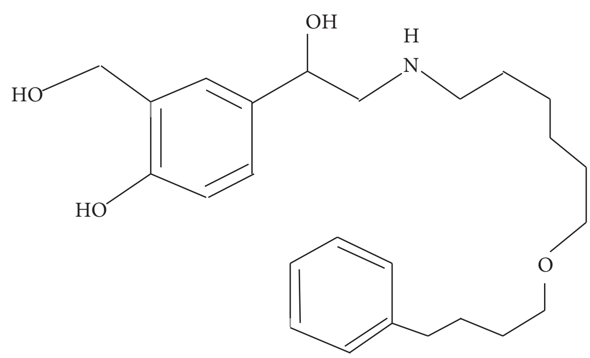

Figure 1: Chemical structure of salmeterol.

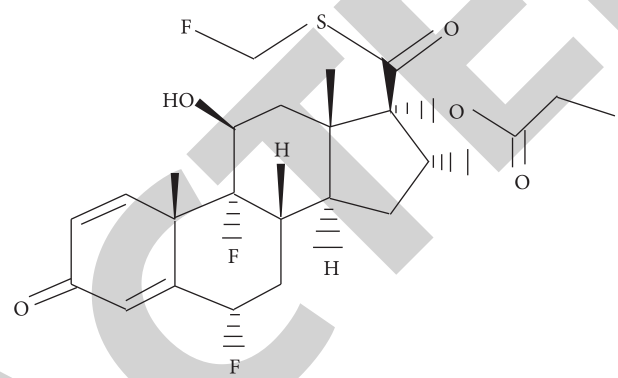

Figure 2: Chemical structure of fluticasone propionate.

4. Fluticasone Propionate

Fluticasone propionate (FP), the chemical structure shown in Figure 2, as corticosteroids.

4.1. FP Metabolism. Scientific research observed that fluticasone propionate, a flunisolide analogue, is only oxidised by 17β-carboxy fluticasone propionate [21]. Nonetheless, more recent research work where fluticasone furoate was analysed, it was found that a number of faecal metabolites were hydroxylated and defluorinated [22]. Consequently, the inference was that FP was metabolised by hydroxylation and oxidative defluorination by CYP3A enzymes. Fluticasone propionate incubations analysis detected the reported 17β-carboxy fluticasone metabolite. There were no any other additional metabolites detected. A fascinating result, without supplying NADPH, FP incubation with either human liver microsomes or CYP3A supersomes did not form any 17β-carboxy fluticasone propionate. This implies that enzymes that belong to esterases do not cut thioester linkages of FP but the hydrolysis is done by the P450 enzymes selectively [23].

4.2. Mode of Action. FP is a corticosteroid that imposes direct and local effects of anti-inflammatory activity and vasoconstriction. Glucocorticoids in general, inhibit the initial inflammatory phenomena like vasodilation, vascular permeability, and leukocyte emigration [24]. Fluticasone cut down inflammatory cells such as eosinophils, monocytes, mast cells, macrophages, dendritic cells, and cytokines produced by these cells. In addition, the drug escalates beta-2 receptors on airway smooth muscle and mitigates mucus gland secretions [25]. Moreover, the medicine cause increments in the anti-inflammatory effects of molecules, namely, annexin-1, secretory leukoprotease inhibitor (SLPI), mitogen-activated kinase phosphatase-1 (MKP-1), glucocorticoid-induced leucine zipper protein (GILZ), and I-kappa B-alpha and inhibitor of NF-kappa B [25].

4.3. Administration. Spray-drying technology has been used for the powder production [26, 27]. Local adverse effects, namely, cough, pneumonia, dysphonia, and oropharyngeal candidiasis are known. Systemic side effects like adrenal suppression, growth suppression, bruising, osteoporosis, cataracts, glaucoma, metabolic abnormalities, and psychiatric disturbances are reported [25].

4.4. Toxicity. There is a report of significant lactic acidosis following an overdose of inhaled salmeterol and fluticasone. The patient inhaled 60 puffs of the drug combination during a suicide attempt and presented with sympathomimetic syndrome, metabolic acidosis, and hyperlactatemia. The patient was proffered a supportive therapy and was within normal health limits the following day. This clinical presentation is ambiguous and supported the idea that fluticasone is a relatively safe drug [19].

4.5. FP Monitoring. Individuals on fluticasone medication ought to undergo monitoring to circumvent the adverse effects. Practitioners should pay attention to any of the side effects described above. In a number of studies, it was observed that stunted growth was permanent in children who were prescribed budesonide. In contrast to budesonide, infants who were under fluticasone prescription had a long-lasting stunted growth effect but potentially not permanent. High doses of ICS are associated with decreased bone density in children. Therefore, children's growth should be monitored regularly on yearly basis [28].

5. Conclusion

Salmeterol/fluticasone propionate is a great combination therapy for COPD and asthma having good indications and prescriptions. The treatment available for the duo are inhaled corticosteroids (ICS). The ICS can work synergically with LABAS (long-acting β_2-antagonists) and so many other medicines like bronchodilators. The drugs used for the treatment of asthma and COPD are metabolised once in the body system, and at the same time, exerting the therapeutic effect provided the concentration of the drug is within the therapeutic window. The CYP3A isoforms metabolise the ICS; in this case, salmeterol and fluticasone propionate (FP). Methods of administration are not limited to inhalation. Specific doses are prescribed accurately paying attention to factors like age, gender, race, and genetic makeup since these affect drug metabolisms. Generally, the ICS work by translocating glucocorticoid receptors to the nucleus from the cytosol. The mechanism is potentiated by the β-antagonists and this brings about an anti-inflammatory effect which is greater than either of the two drugs alone. Once this happens, it is not necessary to increase ICS dose. The ICS, in addition, cause more production of β-receptors by activating the β-receptor genes. This mode of action begets the LABAs' bronchodilator effects. The challenge is that ICS are not limited only to "double" therapy. Analysing such therapies is daunting since coadministration interferes with pharmacology and pharmacokinetics of drugs.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

HM and RA contributed to conception and design of the study and wrote the first draft of the manuscript. NT, LC, SK, RG, MP, AA, DTH, and TNV contributed to the data collection and analysis. All authors approved the submitted version.

Acknowledgments

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