

Research Article



A Respiratory Pharmacological Correlational Analytical Research Study on the Quantification of Drug Safety Levels and Patient Adherence to the Tertiary Treatment with Bronchodilator Drugs

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ABSTRACT

β_2 adrenergic receptor agonists, like salbutamol, formoterol, salmeterol and other β adrenergic agonists, are always the first-line treatment for the reduction of the bronchoconstriction associated with bronchial asthma and chronic obstructive pulmonary disease. The objective of this respiratory pharmacological correlational analytical research study was the quantification of drug safety levels and patient adherence to the tertiary treatment with bronchodilator drugs. This study has shown that the inhaled β_2 adrenergic agonistic bronchodilators were very safe and well-tolerated treatment among the asthmatic patients, with sufficiently high patient treatment compliance and adherence.

Keywords: Clinical Research, Correlational Analytical Research, Quantification, Drug Safety, Patient Adherence, Bronchodilators, β_2 adrenergic receptor agonists.

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INTRODUCTION

β_2 adrenergic receptor agonists, like salbutamol, formoterol, salmeterol and other β adrenergic agonists, are always the first-line treatment for the reduction of the bronchoconstriction associated with bronchial asthma and chronic obstructive pulmonary disease. The β_2 adrenergic receptor agonistic bronchodilators produce bronchodilation among routinely treated asthmatic patients, belonging to almost all the grades of asthmatic attacks, spanning widely from the relief of acute to even chronic bronchospasm, in varying degrees. The newer long-acting bronchodilators, possess the obvious advantage of a prolonged duration of action, thus decreasing the dose administration frequencies. This enhances the convenience and ease of drug administration among the patients suffering from asthmatic bronchoconstriction, improves the drug safety levels by reduction of the bronchodilator associated adverse effects arising from frequent drug administration, and increases

the adherence of the patients to the administered anti-asthmatic treatment. The drug safety levels of the β_2 adrenergic agonistic bronchodilators had always been observed to be much better than any other class of bronchodilator, in routine treatment.

Objectives

The objective of this respiratory pharmacological correlational analytical research study was the quantification of drug safety levels and patient adherence to the tertiary treatment with bronchodilator drugs.

MATERIALS AND METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. Informed consent was obtained.

Study Type

It was a global, multi-centre, prospective, correlational, analytical, open-labelled study.



Study Population

The study population consisted of 43 global mild to early moderate bronchial asthmatic patients.

Selection Criteria of the patients

The inclusion criteria were as follows:

(i) patients of any gender, (ii) patients within 21 and 43 years, (iii) patients suffering from mild to moderate bronchial asthmatic patients, (iv) co-operative and conscious patients, (v) patients willing to undergo all pre and post-treatment investigations and willing to complete the entire course of treatment, (vi) patients who have given consent and are willing to go for a follow-up, (viii) patients not taking any previously started or any concomitant medication.

The exclusion criteria as follows:

(i) uncooperative or unconscious patients, (ii) patients below 21 and above 43 years, (iii) patients presenting with any disease other than mild to moderate bronchial asthma, (iv) patients with a history of hypersensitivity to any of the study drugs, (v) patients with high risk diseases, cardiac, renal or any other associated complications or co-morbidities, (vi) any chronic disease intervening with the study data, (vii) immunocompromised patients, (viii) patients suffering from gastrointestinal diseases like peptic ulcer, regional enteritis and ulcerative colitis, (ix) pregnant or lactating women (women of child bearing potential are required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of study), (x) children or very old patients, (xi) other associated medical illness or disorders having impact on study results.

Study Period

The study period, comprising of the periods for the research study and the compilation of the study literature, was 1 year, July, 2013 to September, 2013, and from June, 2021 to February, 2022.

Study Place

The research study and the compilation of the study literature was done in the Departments of Pharmacology, Clinical Pharmacology, Evidence-Based Medicine, Respiratory Medicine, Molecular Medicine, and Clinical Research, in Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Mamata Medical College and Hospitals, Rama Medical College Hospital and Research Centre, Rama University, J. J. M. Medical College and Hospitals, Chigateri General Hospital, and Mahuya Diagnostic Centre and Doctors' Chamber.

Study Procedure

43 global patients, with mild to early moderate asthma, were selected for this research study. After obtaining the clearance from the Institutional Ethics Committee and

informed consent, the following data of the thorough patients' history with complete examination details and prescription patterns were obtained with the study proforma: the demographic characteristics, including age, gender, race, body mass index, duration of symptoms of asthma, severity of asthma symptoms, present controller medications, the patients' present and past history, smoking history, respiratory history including respiratory immunological history and history of allergy, chronic obstructive pulmonary disease and asthma, cardiac history, history of co-morbidities, family history, personal history, socio-economic history, reproductive history, concomitant medication history, and surgical history were recorded. The Saint George's Respiratory Questionnaire (SGRQ) scores, and the Baseline Dyspnoea Index (BDI) / Transition Dyspnoea Index (TDI) questionnaire scores, were recorded, to assess the effect of treatment on asthma. Details of complete general physical examination, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory and cardio-pulmonary examinations, were recorded. Pulse rate, oxygen saturation of arterial haemoglobin (SpO₂) and respiratory rate were recorded with a Peak Flow Meter. Spirometric variables like peak expiratory flow rate (PEFR), forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC, were recorded, after giving bronchodilators, by metered dose inhaler. The patients were prescribed the treatment of inhaled bronchodilators with a metered dose inhaler, 2 puffs in each nostril, once in the early morning, and once in the early evening, for the required treatment time-schedules, depending on the progressing disease severity and prognosis, of the asthmatic patients. After each inhalation dose, the patients were monitored for 24 hours, for the occurrence of any adverse effect, like headache, tremor, irritation in the oral cavity and palpitation, with Adverse Event Case Report Forms. The study findings were recorded and thoroughly analysed. Then the drug safety levels of the bronchodilators was quantitatively appraised. The patients' participation assessment and the adherence of the asthmatic patients to the tertiary bronchodilator treatment was done by recording and thoroughly analysing the total number of patient participants, the total number of patients who completed the study thoroughly, the total number of drop-out patients due to adverse effects, the total number of patients who were lost to follow-up and the total number of patients who withdrew voluntarily.

Statistical analysis

The study findings were statistically analysed, with tabular illustrations, along with the test of significance, being denoted by the p-value (p-value ≤ 0.05: statistically significant), and subsequent graphical illustrations, in percentages.

RESULTS

In this study, the demographic patient characteristics were comparable. There were no occurrence of any adverse drug reaction with the inhaled β₂ adrenergic agonistic



bronchodilators, 2 puffs in each nostril twice a day, as shown in Table 1. The adverse effects of the bronchodilators were not statistically significant, and the inhalation of the bronchodilators, were safe and tolerable.

Therefore, on graphical illustration, as shown in Figure 2, the drug safety level was 100% for the inhaled β_2 adrenergic agonistic bronchodilators.

Table 1: Adverse Drug Reactions of Bronchodilators and their Frequency

Sl. No.	Adverse drug reactions of bronchodilators 2 puffs in each nostril BD	Number of patient occurrence of adverse drug reactions (n=43)	p-value
1.	Headache	0	Non-significant
2.	Tremor	0	Non-significant
3.	Irritation in oral cavity	0	Non-significant
4.	Palpitation	0	Non-significant

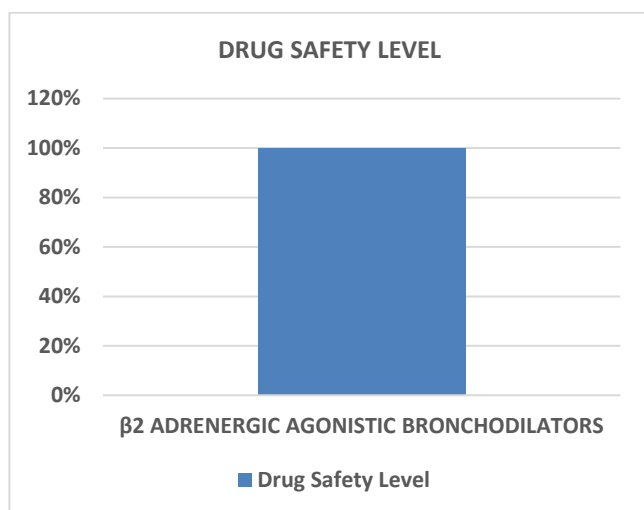


Figure 1: Drug Safety Levels of β_2 Adrenergic Agonistic Bronchodilators

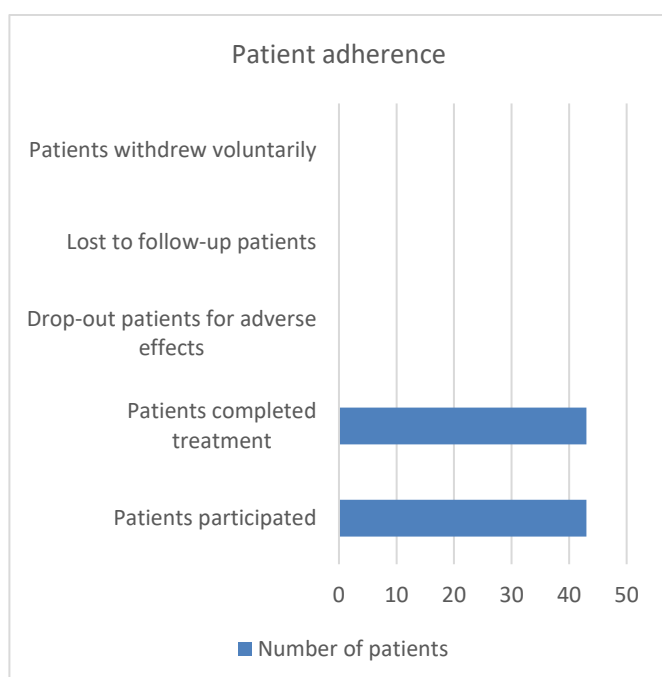


Figure 2: Patient Adherence to β_2 Adrenergic Agonistic Bronchodilators

As for the patients' participation assessment and the adherence of the asthmatic patients to the bronchodilator treatment, as shown in Figure 2, 43 global asthmatic patients suffering from mild to early moderate asthma, had participated in the study. All the patients completed the treatment thoroughly. There were no drop-out patients due to adverse effects, none was lost to follow-up and none of the patients withdrew voluntarily. Therefore, the patients' adherence to treatment was very high.

DISCUSSION

Among the wide ranges of β_2 agonists, the short-acting β_2 agonists, salbutamol, terbutaline, levalbuterol and pirbuterol, have the shortest half-life, short duration of action and cause immediate relief of acute symptoms; the long-acting β_2 agonists, salmeterol, formoterol, have a long half-life, long duration of action and cause a prolonged relief of symptoms; and the ultra-long-acting β_2 agonists, indacaterol, olodaterol, vilanterol, formoterol, have the longest of half-lives, longer duration of action and cause a sustained symptomatic relief. The prolonged duration of action of the long-acting and ultra-long-acting β_2 agonists is effected by the decrease in the susceptibility of β_2 agonists to catechol O-methyl transferase and monoxidase enzymes which initiates oxidative deamination and methylation for inactivating β_2 agonists.

The selective liganding of β_2 agonists to the adrenergic receptors, causes the activation of the β_2 adrenergic receptors. This activates a transmembrane signal cascade involving the G protein Gs and adenylyl cyclase, which acts as the effector. Subsequently, adenylyl cyclase increases the intracellular cAMP by ATP hydrolysis. The elevated levels of cAMP activates the cAMP dependent protein kinase A, which in turn phosphorylates the intracellular substrates, resulting in various pharmacological and cellular responses. These responses are mediated by the cascade of intracellular pharmacodynamic signals caused by the phosphorylation of Gq coupled receptors through the action of protein kinase A in the bronchial smooth muscles. This causes a reduction in the intracellular Ca^{2+} and also decrease the sensitivity of Ca^{2+} . The change in the Ca^{2+} levels inhibits the myosin light chain phosphorylation,

which prevents the bronchial smooth muscle contraction and causes bronchodilatation. β_2 agonists also has bronchial smooth muscular anti-inflammatory activity. This is caused due to the inhibition of different inflammatory pharmacodynamic mechanisms, brought about by the reduction of intercellular adhesion molecule-1, reduced release of granulocyte-macrophage colony-stimulating factors, and stabilisation of mast cell degranulation.¹⁻⁴

In this study, it was found that the demographic patient characteristics were comparable. As there were no occurrence of any adverse drug reaction with the inhaled β_2 adrenergic agonistic bronchodilators, administered 2 puffs in each nostril twice a day, depending on the progressing disease severity and prognosis, of the asthmatic patients, and the adverse effects of the bronchodilators were not statistically significant, thus, the inhalation of the bronchodilators, were safe and tolerable, among the mild to early moderate asthmatic patients. The drug safety levels was found to be 100% for the inhaled β_2 adrenergic agonistic bronchodilators, proving the bronchodilators to be very safe for the treatment of the asthmatic patients. As for the asthmatic patients' participation assessment and the adherence to the bronchodilator treatment, 43 global asthmatic patients suffering from mild to early moderate asthma, had participated in the study; all the patients completed the treatment thoroughly; there were no drop-out patients due to adverse effects; none was lost to follow-up and none of the patients withdrew voluntarily. Therefore, the patients' adherence to treatment was very high.

CONCLUSIONS

Therefore, this study has shown that the inhaled β_2 adrenergic agonistic bronchodilators were very safe and well-tolerated treatment among the asthmatic patients, with sufficiently high patient treatment compliance and adherence.

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