

## A pharmacoepidemiological study of prescription patterns of $\beta_2$ sympathomimetic bronchodilators in exacerbation of non-severe asthma in tertiary care hospitals, not needing hospitalization

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### ABSTRACT

**Background:** Arformoterol, the (R, R) enantiomer of the racemic (R, R / S, S) diastereomer, formoterol, is a short and long acting  $\beta_2$  agonist bronchodilator. Levosalbutamol, the (R, R) enantiomer of racemic diastereomer (R, R / S, S) salbutamol, has a greater affinity for the  $\beta_2$  receptor. Occupation of  $\beta_2$  receptors by agonists result in the activation of the Gs-adenylyl cyclase-cAMP-PKA pathway, followed by phosphorylative events leading to bronchial smooth muscle relaxation. The aim of this pharmacoepidemiological study was to analyse the prescription patterns, and prescription content analysis, of arformoterol, levosalbutamol, formoterol or salbutamol, in non-severe asthma exacerbation in tertiary care hospitals, not needing hospitalization.

**Methods:** It was a multi-centre, retrospective, observational and analytical study of 100 asthmatic patients' hospital medical records, treated with 3 doses of arformoterol, levosalbutamol, formoterol or salbutamol nebulization, followed by peak expiratory flow rates (PEFR) measurement at the baseline and 6 minutes, after each dose; along with adverse effects recording. The number of prescriptions of 100 patients was recorded, the percentage of prescriptions was calculated, and the prescription content analysis was done.

**Results:** PEFR of the patients showed significant increase after the first, second and third doses of bronchodilator nebulisation, with negligible adverse effects. Salbutamol was most commonly prescribed (45 prescriptions, 45%), followed by levosalbutamol (35 prescriptions, 35%), formoterol (15 prescriptions, 15%) and arformoterol (5 prescriptions, 5%). All aspects of prescription content analysis showed 100% completeness.

**Conclusions:** Arformoterol was more effective, but equally safe, as compared to levosalbutamol, formoterol and salbutamol. Prescription frequency of salbutamol was followed by levosalbutamol, formoterol and arformoterol. Prescription content analyses showed 100% completeness.

**Keywords:** Prescription patterns, Arformoterol, Levosalbutamol, Salbutamol, Formoterol, Non-severe asthma

### INTRODUCTION

Asthma is a global health problem affecting around 300 million individuals of all ages, ethnic groups and countries.<sup>1</sup> Asthma is a chronic inflammatory disease of the airways, characterized by increased bronchial hyperresponsiveness, bronchoconstriction, microvascular leakage and plasma exudation, due to activation of  $M_3$  receptors on bronchial smooth muscle by increased cGMP levels, on release of acetylcholine, caused by released histamine, leukotriene  $C_4$ ,  $D_4$ ,  $B_4$ , prostaglandin  $D_2$ , protease enzymes,  $TNF\alpha$ , platelet activating factor,

interleukins (IL-4, IL-5, IL-13), adenosine, eosinophil cationic protein, neuropeptides (substance-P and neurokinin-A), from the allergen induced activated mast cells, infiltrating eosinophils, basophils and T helper 2 lymphocytes. The symptoms of asthma are breathlessness, wheezing, cough, and chest tightness at night and in early morning.<sup>2</sup> Non-severe asthma, if mild, is defined as the degree of asthmatic severity, wherein patients are dyspnoeic only with activity, with a peak expiratory flow (PEF)  $\geq 70\%$  of predicted or personal best and  $SpO_2 > 90\%$ ; and, if moderate, is defined as the degree of asthmatic severity, wherein patients are

dyspnoeic, which interferes or limits their usual activity, with a PEF 40-69% of predicted or personal best and SpO<sub>2</sub> >90% [unlike, severe asthma, which is defined as the “uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)”].<sup>1</sup> Worldwide, asthmatic morbidity and the associated mortality, is threatening.<sup>3</sup>

The different  $\beta_2$  sympathomimetic bronchodilators are short-acting  $\beta_2$  agonists like salbutamol, levosalbutamol, metaproterenol, terbutaline, rimiterol, fenoterol, tulobuterol, and pirbuterol; long-acting  $\beta_2$  agonists like salmeterol, formoterol, and arformoterol; and ultra-long-acting  $\beta_2$  agonists like indacaterol, carmoterol, milveterol, GSK-642444, BI-1744-CL, LAS-100977, and PF-00610355.<sup>4</sup>

Occupation of  $\beta_2$  receptors by agonists result in the activation of the G<sub>s</sub>-adenylyl cyclase-cAMP-PKA pathway, resulting in phosphorylative events leading to bronchial smooth muscle relaxation, by the following molecular mechanisms :

- Lowering of [Ca<sup>2+</sup>]<sub>i</sub> concentration by active removal of Ca<sup>2+</sup> from the cytosol into intracellular stores and out of the cell.
- Acute inhibition of the PLC-IP<sub>3</sub> pathway and its mobilization of cellular Ca<sup>2+</sup>.
- Inhibition of myosin light chain kinase activation.
- Activation of myosin light chain phosphatase.
- Opening of a large conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channel (K<sub>Ca</sub>), which repolarizes the smooth muscle cell and may stimulate the sequestration of Ca<sup>2+</sup> into intracellular stores.  $\beta_2$  receptors may also couple to K<sub>Ca</sub> via G<sub>s</sub> (stimulatory G protein) so that relaxation of airway smooth muscle may occur independently of an increase in cAMP.
- Increased Na<sup>+</sup>/Ca<sup>2+</sup> exchange.
- Increased Na<sup>+</sup>, Ca<sup>2+</sup> - ATPase activity.

The  $\beta_2$  sympathomimetic bronchodilators inhibit the release of bronchoconstrictor mediators from inflammatory cells and of bronchoconstrictor neurotransmitters from airway nerves, by the following mechanisms :

- Prevention of mediator release from isolated human lung mast cells (via  $\beta_2$  receptors).
- Prevention of microvascular leakage and thus the development of bronchial mucosal oedema after exposure to mediators, such as histamine and leukotriene D<sub>4</sub>.
- Increase in mucus secretion from submucosal glands and ion transport across airway epithelium; these effects may enhance mucociliary clearance, and thereby reverse the defective clearance found in asthma.

- Reduction in neurotransmission in human airway cholinergic nerves by an action at presynaptic  $\beta_2$  receptors to inhibit acetylcholine release. This may contribute to their bronchodilator effect by reducing reflex cholinergic bronchoconstriction.<sup>2</sup>

Arformoterol is the (R, R) enantiomer of formoterol, a short and long acting  $\beta_2$  agonist bronchodilator and is distinguishable from the most commonly used racemic (R, R / S, S) diastereomer of formoterol. *In vitro* data show significant bronchodilatation, inhibition of inflammation and marked baseline airway reversibility with arformoterol.<sup>5,6</sup> Salbutamol is the most common  $\beta_2$  agonist being currently used in the treatment of asthma. It is a racemate, and a 1:1 mixture of the dextro [(S)-salbutamol] and levo [(R)-salbutamol] rotatory forms.<sup>7</sup> Levosalbutamol is the purified enantiomer of racemic salbutamol (both R and S) that has a greater affinity for the  $\beta_2$  receptor as compared to (S)-salbutamol. Levosalbutamol is a single isomer  $\beta_2$ -agonist that differs from racemic salbutamol by the elimination of (S)-salbutamol. Formoterol is a unique  $\beta_2$  agonist, being both rapid and long acting.<sup>8,9</sup> There are few demonstrations of formoterol being more efficacious when compared to salbutamol; and both the therapies being well-tolerated.<sup>10,11</sup> The enantiomers of  $\beta_2$ -agonists in the R configuration are primarily responsible for the bronchodilating effects of the racemate. The plasma concentrations of the enantiomers of anti-asthma drugs may differ as a reflection of stereoselectivity in clearance, volume of distribution, and route of administration.<sup>12</sup> With  $\beta$ -agonists being the most widely used agents in the treatment of asthma, *in vitro* studies reported that  $\beta$ -adrenergic receptor (ADRB2) polymorphisms are associated with agonist-promoted down-regulation. Non-synonymous single nucleotide polymorphisms (SNPs) of ADRB2 at codons 16 and 27 are significant.<sup>13</sup>

The aim of this pharmacoepidemiological study was to analyse the prescription patterns of different of  $\beta_2$  sympathomimetic bronchodilators, like arformoterol, levosalbutamol, formoterol or salbutamol, in the exacerbation of non-severe asthma in tertiary care hospitals, not needing hospitalization; because there is a dearth of relevant study literature.

## METHODS

### Study type

It was a multi-centre, retrospective, observational and analytical study of the hospital medical records.

### Study population

100 patients, who had earlier attended the respiratory Medicine out-patients departments of tertiary care hospitals, and were treated for exacerbation of non-severe asthma, not needing hospitalisation.

### **Study place**

Departments of Pharmacology and Respiratory Medicine of Gouri Devi Institute of Medical Sciences and Hospital, Durgapur, West Bengal, India; J. J. M. Medical College, Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka, India; and departments of Clinical Pharmacology and Respiratory Medicine of Hazra Polyclinic and Diagnostic Centre, Hazra Nursing Home, Domjur, Howrah, Kolkata, West Bengal, India.

### **Study period**

5 months (the research study was conducted within the months of September 2012 to January 2013 and the compilation of the study literature was done within the months of March-April, 2017).

### **Selection criteria of the patients**

The patients were selected based on the inclusion and the exclusion criteria given below, and the patients fulfilling those criteria, were included in the study.

### **Inclusion criteria**

The inclusion criteria were patients' age >18 years, and of either sex, British Thoracic Society definition of acute non-severe asthma, patients' ability to perform forced expiratory manoeuvre, and co-operative and conscious patients.<sup>14</sup>

### **Exclusion criteria**

The exclusion criteria were uncooperative and unconscious patients, patients presenting with acute severe or acute life-threatening or near-fatal asthma, history of hypersensitivity to the study drugs, pregnant or lactating women, other associated medical illness having impact on study results and children or very old patients.

### **Ethical approval**

At first, the clearance and the approval from the Institutional Ethics Committee were obtained. The study was conducted in accordance with the ethical principles originating from the 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 in compliance with the regulatory requirements. Written permissions to access the relevant hospital medical records were obtained from the hospitals, outlining the aims of the study. The study involved almost negligible risk, of any type, to the patients. The design provided an equal opportunity to all the eligible patients treated for non-severe asthma to be included in the study. The patients who were included in the study were assured confidentiality, and an informed consent was obtained from each individual.

### **Methodological procedure**

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, from the hospital medical records of the patients treated for exacerbation of non-severe asthma, not needing hospitalization: the patients' participation assessment and adherence to treatment (including patients who completed the study thoroughly, number of drop-out patients to adverse effects, patients who were lost to follow-up and patients who withdrew voluntarily); 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 Dyspnea Index (BDI) / Transition Dyspnea Index (TDI) questionnaire scores, were recorded, to assess the effect of treatment on asthma.<sup>15</sup> Details of complete general physical examination, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory and cardio-pulmonary examinations, were recorded. Pulse rate and oxygen saturation of arterial haemoglobin (SpO<sub>2</sub>) measurements with pulse oximeter, and respiratory rate were recorded. Using a peak flow meter (Breath-O-Meter), the baseline peak expiratory flow rate (PEFR) was measured. Peak expiratory flow rates were measured at the baseline and 6 min, after each dose. The 100 patients were treated with (i) 3 doses of nebulization with 15 µg arformoterol respules (totally 45 µg), through oxygen driven (6 L/min) nebulizer, three times a day, or, (ii) 3 doses of nebulization with 0.63 mg levosalbutamol respules (totally 1.89 gm), with the same nebulizer, three times a day, or, (iii) 3 doses of nebulization with 15 µg formoterol respules (totally 45 µg), with the same nebulizer, three times a day, or, (iv) 3 doses of nebulization with 5 mg salbutamol respules (totally 15 mg), with the same nebulizer, three times a day. Corticosteroid was added to the nebulization, after the third dose of the drug was administered, to eliminate the impact of other drugs on the treatment outcome. 6 minutes after administering each dose of the bronchodilators, PEFR was measured. Best of the three PEFR measurements was recorded, at each recording. After the third dose, patients were followed up for a period of 10 hours, for the occurrence of any adverse effect. To evaluate the significant improvement in either group, one sample test was used to compare the PEFR before and after each dose of the drug. The prescription patterns of all 4 drugs were analysed. The number of prescriptions of 100 patients treated with each drug:

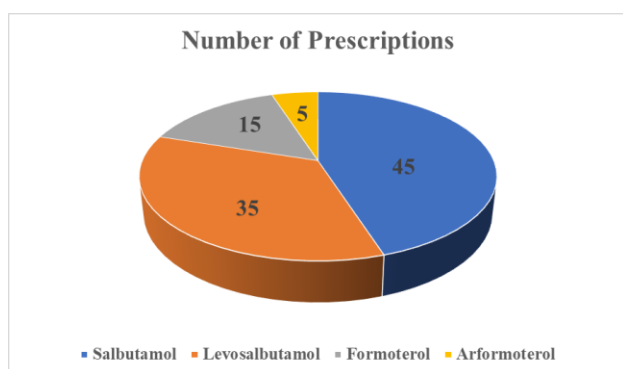
arformoterol, levosalbutamol, formoterol or salbutamol was recorded, and the percentage of prescriptions for each drug was calculated. The prescription content analysis, of all the 100 prescriptions, was done. The different aspects of prescription content analysis were: (i) completeness of prescription contents, (ii) mention of the dose of drug, (iii) mention of the duration of treatment, (iv) mention of the instructions of medication, (v) mention of the frequency of drug intake, (vi) mention of the name of the drug, and, (vii) mention of the dosage form of the drug. The study data obtained were recorded in details and thoroughly analysed.

**Statistical analysis**

The study data were statistically analysed with different percentages.

**RESULTS**

100 patients were treated for exacerbation of non-severe asthma, not needing hospitalisation. 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. The patients’ adherence to treatment was very high. The demographic characteristics and the baseline PEFr for arformoterol, levosalbutamol, formoterol or salbutamol were comparable. For all the 4 drugs, PEFr showed significant increase compared to the baseline values and there was increase after each dose of the drug. The increases in PEFr after the first, second and the third dose were significantly more with arformoterol than that with levosalbutamol, followed by formoterol and salbutamol (arformoterol > levosalbutamol > formoterol = salbutamol). Adverse effects were negligible in either group. Tolerability was good for both the drugs.



**Figure 1: Prescription rates of different β<sub>2</sub> sympathomimetic bronchodilators in percentages.**

Figure 1 depicts the prescription rates of different β<sub>2</sub> sympathomimetic bronchodilators in percentages. Salbutamol was most commonly prescribed significantly (45 prescriptions, 45%), followed by levosalbutamol (35 prescriptions, 35%), formoterol (15 prescriptions, 15%), and arformoterol (5 prescriptions, 5%).

and arformoterol (5 prescriptions, 5%) (salbutamol > levosalbutamol > formoterol > arformoterol).

**Table 1: Prescription content analysis for different β<sub>2</sub> sympathomimetic bronchodilators.**

Prescription contents	Result (%)
Completeness of prescription contents	100 (100)
Dose of drug	100 (100)
Duration of treatment	100 (100)
Instructions of medication	100 (100)
Frequency of drug intake	100 (100)
Name of the drug	100 (100)
Dosage form of the drug	100 (100)

Table 1 depicts the prescription content analysis in percentages for different β<sub>2</sub> sympathomimetic bronchodilators. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions.

**DISCUSSION**

In the global public health scenario, asthma still holds an extremely significant position.<sup>16</sup> This study has shown amply comparable results, with no statistically significant difference among the demographic characteristics and the clinical criteria of the patients nebulized with arformoterol, levosalbutamol, formoterol or salbutamol. It was observed that there was an overall increase in the prevalence of the exacerbations of non-severe asthma, among the women, compared to men, with increasing age.

Among the 100 patients with non-severe asthma, the average duration of symptoms was found to be moderately long; there was a visible increase in the pulse rates and respiratory rates; but oxygen saturation was almost within the normal range. The baseline PEFr were also comparable, among the patients nebulized with arformoterol, levosalbutamol, formoterol or salbutamol. PEFr of the patients showed significant increase compared to the baseline values and there was significant increase after each dose of the drugs given. The increases in PEFr after the first, second and the third doses were significantly more with arformoterol nebulization than with that of levosalbutamol, followed by formoterol and salbutamol. Hence, nebulization with arformoterol was observed to be more efficacious than with that of levosalbutamol, followed by formoterol and salbutamol, as a rescue medication, in exacerbation of non-severe asthma. An analysis of the prescription patterns showed that salbutamol was most commonly prescribed significantly (45 prescriptions, 45%), followed by levosalbutamol (35 prescriptions, 35%), formoterol (15 prescriptions, 15%) and arformoterol (5 prescriptions, 5%). The completeness of prescription contents, the dose

of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions.

As a starter bronchodilator in acute asthma, short-acting  $\beta_2$  agonists, such as salbutamol, are considered better, for their rapid onset of action. But, these have to be frequently administered, due to their short duration of action, which often causes inconvenience among the patients.<sup>17</sup> Usefulness of long-acting beta-2 agonists such as salmeterol and formoterol as rescue medication in exacerbations of asthma was recently recognized.<sup>18</sup> As a clinically favorable bronchodilator, formoterol have both a rapid onset and long duration of action, with a well-charted safety and tolerability profile.<sup>19</sup> So it can ideally be used as an alternative to short-acting  $\beta_2$  agonists in the management of exacerbations of acute asthma as it causes rapid bronchodilatation, while reducing the need for frequent administration. Being hydrophilic drugs, salbutamol has an ability to reach the  $\beta_2$  receptor from the aqueous phase, thus showing rapid onset of action while, formoterol is much more lipophilic than salbutamol. The aqueous part rapidly activates the  $\beta_2$  receptor, whereas the lipophilic part is taken up into the cell membrane from which it diffuses slowly and thus stimulates  $\beta_2$  receptor over a prolonged period. This action results in rapid onset along with a long duration of action of formoterol, just as demonstrated in the study.<sup>20-22</sup> Just as salbutamol, onset of action of formoterol is 1-3 min; and after 5-10 min of inhalation, 80-90% of the bronchodilatation occurs; duration of action being 12 hours.<sup>19</sup> The other effects of formoterol on the airway, apart from bronchodilatation, are the inhibition of plasma leakage in the airways through the beta-2 receptor on the endothelial cells of post-capillary venules and sputum  $\alpha$ -2 macro-globulin; and the inhibition of mediator release by mast cells, which is an important benefit in the treatment of asthma.<sup>16,23-26</sup> Neutrophils are the key inflammatory cells in COPD.<sup>16</sup> Beta-2-adrenoceptors are expressed on human neutrophils and beta-2-agonists inhibit the release of reactive oxygen species.<sup>16,27</sup> Some studies have also shown that LABAs (long acting beta agonists) decrease bronchial neutrophils.<sup>16,28,29</sup> The efficacy of long-acting beta-2 agonists, such as salmeterol and formoterol, in the maintenance therapy of chronic stable asthma (when used along with an inhaled corticosteroid) and also in acute non-severe asthma, acute severe asthma, exercise induced bronchospasm, childhood asthma and COPD are well-documented.<sup>10,18,19,30</sup> Most studies show the use of formoterol with terbuhaler, aerolizer, or metered dose inhaler. But, there are very less studies showing the use of formoterol in the form of nebulization.<sup>19</sup> Arformoterol can be used in patients who are unable or unwilling to use a dry powder inhalation (DPI) or metered dose inhaler (MDI) preparation. Other uses of arformoterol nebulized medication are seen in patients who have repeated episodes of airflow obstruction despite DPI / MDI use and in patients with severe lung function compromise.<sup>31</sup> In some of the short and long term clinical trials, the efficacy

of inhaled formoterol has been equal to or greater than that of salbutamol, fenoterol and terbutaline.<sup>20</sup> Recent studies have shown that when inhaled formoterol 12 or 24  $\mu$ g twice daily was added to the existing inhaled corticosteroid, it improved lung function and reduced asthma symptoms, compared to placebo. Formoterol has got significant therapeutic advantages over shorter-acting beta 2-agonists in the treatment of nocturnal and exercise-induced asthma, as it reduces the need for reliever medication, due to its longer duration of action. When administered 3 and 12 hours before exercise, formoterol conferred more protection than salbutamol. Formoterol is currently recommended for use as an alternative medication to increasing inhaled steroid dosage, in patients whose asthmatic symptoms are inadequately controlled despite therapy, with low to moderate doses of inhaled steroids and intermittent short-acting beta 2-agonists.<sup>32</sup> Oral irritation was found to be a common adverse effect of arformoterol, while with salbutamol - headache, palpitation, oral irritation and tremors were the adverse effects; although there was no statistically significant difference in the adverse effects, among the 4 groups of medications, and these were found to be mild and very few. Hence, arformoterol nebulization was observed to be as safe as levosalbutamol, formoterol or salbutamol nebulization, in the rescue therapy of the exacerbation of non-severe asthma. Evidence of safety of formoterol is also available in the study-literature, even at high doses in patients with asthma and COPD.<sup>33</sup> As there are significantly fewer clinical data available on the use of arformoterol, the safety of this nebulized drug has not been as clearly established as that of racemic formoterol. In a study, dryness of mouth was the commonly reported side effect of formoterol inhalation.<sup>30</sup> Few clinical trials exhibit good tolerability of arformoterol.<sup>34,35</sup> A study on the use of racemic formoterol and arformoterol in asthma found that both the drugs were well tolerated.<sup>36</sup>

This pharmacoepidemiological study would remain a milestone in the development of newer respiratory, smooth muscular and anti-inflammatory diagnostics and therapeutics; in the development of faster, better, safer, more precise and cost-effective therapeutics; in the cure of patients suffering from asthma; and, finally in the enhancement of respiratory health, healthy life, quality of life, facial beauty and life span, among the generations to come.

## CONCLUSION

Arformoterol was more effective, but equally safe, as compared to levosalbutamol, formoterol or salbutamol, in the therapy of the exacerbation of non-severe asthma. Salbutamol was most commonly prescribed significantly, followed by levosalbutamol, formoterol or arformoterol. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were observed in 100% of prescriptions.

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