A Cross-sectional Cohort Analyses Assessing Response to Levosalbutamol Bronchodilatory Cough Formulations in Outpatient Community Settings of India: ‘BUS’ analyses

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Abstract

Introduction: Cough is significant health problem with greater implication for impaired quality of life. Acute and chronic cough due to infective (viral/bacterial), allergic conditions or bronchial asthma including cough variant asthma are often treated with combination of mucolytics, expectorants and bronchodilators. Bronchodilators reduces cough sensitivity, promotes clearance of cough secretions while reducing protrusive inflammatory mediator release.

Aims and Objectives: To further understand the clinical utility and safety of Bronchodilatory cough formulations (BCF) containing Levosalbutamol in real world settings.

Material and Method: A prospective, cross sectional, cohort analyses (Bronchodilatory coUgh formulary Survey, BUS) assessing Levosalbutamol cough formulations utilization at 40 centers involving general and consultant physicians across India

Results: Consecutive prescription records (n=1367) involving Levosalbutamol were collated for analyses. Baseline demographics included adults (21%) and children (79%) with mean age 11.1 yrs, male (60%) and female (40%). Levosalbutamol BCF was commonly prescribed for LRTI (69.7%), AECB (14.8%), Bronchial asthma (8.5%), Allergic rhinitis (5%). The predominant risk factors in both adults and children included smoking and allergic rhinitis respectively. In most cases cough severity was assessed utilizing Fisman scale score (0-4). Mean cough score improved from baseline score of 3 to 0.8 with parallel improvement in associated symptoms of wheeze and sputum. Antibiotics were prescribed in most of LRTI or acute exacerbation cases with purulent sputum. Side effects noted included tremor (1%), palpitation (0.9%), vomiting (0.7%) that were mild and transient in most cases with none requiring treatment withdrawal. In two cases (0.1%), further treatment with nebulization and antibiotics were provided

Conclusion: Levosalbutamol containing Bronchodilatory Cough formulation remains as safe and effective option for adults and children while managing acute or chronic cough primarily due to allergic rhinitis, bronchial asthma or COPD

Editorial Viewpoint

The study assesses clinical utility of bronchodilatory cough formulations (BCF).

Levosalbutamol as BCF was commonly prescribed for LRTI in 70% of patients.

L e v o s a l b u t a m o l containing BCFs are safe and effective option in the management of acute chronic cough due to allergic rhinitis, bronchial asthma or COPD.

Introduction

Cough is distressing and most common symptom requiring patient to seek medical care in outpatient settings.¹ Acute cough, most common type of cough, leads to significant distress and impaired quality of life.² Chronic cough is responsible for high morbidity, exhaustion, depression up to 53%, insomnia, increased non-working days, urinary incontinence, cough syncope and impaired quality of life.³,⁴

Common causes for Adult cough include, Acute cough [Infectious: URTI (Upper Respiratory

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Received: 08.03.2016; Revised: 10.06.2016; Accepted: 16.06.2016
Tract Infection), LRTI (Lower Respiratory Tract Infection); Exacerbations: Bronchial asthma, COPD (Chronic Obstructive Pulmonary Disease), UACS (Upper Airways Cough Syndrome); Subacute cough [Postinfectious: Pneumonia, Bronchitis; New onset or exacerbation: Bronchial asthma, UACS, GERD (Gastroesophageal Reflux Disease), Bronchitis]; Chronic cough [UACS, Bronchial asthma, GFRD, COPD, pulmonary tuberculosis, interstitial lung disease].

Chronic cough remains a major clinical challenge, both in terms of diagnosis and management strategies due to the overlapping etiological factors that may have been inappropriately or inadequately treated. Most common of them include bronchial asthma, cough variant asthma (CVA) or atopic cough and non-asthmatic eosinophilic bronchitis (NAEB).

Cough in asthma is categorized as Cough variant asthma that presents only with cough or Cough predominant asthma presenting with predominant or persistent cough despite well controlled dyspnea or wheezing. The cough variant asthma or the bronchodilator responsive cough, accounts for nearly 30% of the cough referrals.

Similarly, in respiratory conditions like pneumonia, COPD, Bronchial Asthma, Emphysema, Acute and Chronic bronchitis there is excess mucus production along with some bronchospasm, therefore there is need for a comprehensive formulation that will expel the mucus out of the airways and give symptomatic relief to the patient. Ambroxol is a mucolytic agent which helps in liquefying the thick viscid mucus and also helps to increase the antibiotic penetration in the purulent mucus in respiratory infections. Levosalbutamol is a bronchodilator which helps to dilate the airways to help the expulsion of mucus and also opens the airways since it also offers complimentary action in improving Mucociliary clearance or Ciliary Beat Frequency. At the same time, the Bronchodilator also reduces the release of proinflammatory mediators from mucosal mast cells, thereby offering anti-inflammatory action that is clinically relevant in cases of Allergic cough. Guaiphenesin is an expectorant which helps in getting the sputum out. However, the role of Bronchodilatory cough formulations for acute or chronic cough seems to be underutilized with no clinical documentation on the same.

To further analyze the perceptions, insights, viewpoints on the role of Bronchodilatory Cough formulations in ‘real world’ settings, a cross-sectional survey in the outpatient settings of India was carried out.

Material and Methods

A prospective, cross-sectional survey assessing prescription records of Bronchodilatory Cough formulations were analyzed from 40 outpatient centers with pediatric practice across India. Patients with Cough and monitoring records for at least a week were included. Any Serious adverse event (SAE) defined as medical abnormality or hospitalization, disability, death, congenital anomaly were confirmed to be reported to regional or central Pharmacovigilance center.

Statistical Analyses: Descriptive statistics was used to tabulate the data with percentage rate calculated for all categorical nominal and ordinal data variables.

Results

Bronchodilatory cough formulation prescriptions involving Levosalbutamol (n=1367) were collated for further analyses.

Baseline demographics: The Baseline demographics included male (60%), female (40%) patients with the mean age of distribution as 11.1 yrs. Antibiotics including Beta-lactam/Beta lactamase inhibitor, Cephalosporin, Macrolides or Fluoroquinolones were prescribed for cases predominantly with purulent sputum. In 183 cases (13.3%) of chronic cough, the concomitant therapies included ICS/LABA and/or LTRAs as highlighted in Table 1.

The presenting complaints included cough (92%), rhinorrhea (67%), wheeze (61%), fever (60%) and others (16%) (Figure 1).

Sputum characteristics included

| Table 1: Baseline demographics for patients on bronchodilatory cough formulation containing levosalbutamol |
|---------------------------------|-------------------------------|---------------------|
| Patients (n) | 1367 pts | Mean Weight (kg) | 22.4 |
| Male | 796 | 60% |
| Female | 541 | 40% |
| Mean age (yrs) | 11.1 |
| < 5 yrs | 555 | 41% |
| 5-11 yrs | 528 | 39% |
| ≥ 12 yrs | 281 | 20% |
| Concomitant medications | | |
| ICS/LABA | 101 | 7.3% |
| LTRAs | 34 | 2.5% |

Fig. 1: Clinical signs and symptoms at baseline visit
mucoid (54%) or purulent (22%) expectoration at baseline visit. Concurrent medications included antibiotics (48%) and ICS/LABA therapy for bronchial asthma (10%).

Clinical results: Study cases (n=1367) were diagnosed with LRTI (69.7%), AECB (14.8%), Bronchial asthma (8.5%), Allergic rhinitis (5%) and others including Sinusitis or Tuberculosis (0.3%) by physician (Figure 2).

BCF containing Levosalbutamol was usually prescribed for a week (94%) before further follow-up as requested by the physician. Concurrent antibiotics were prescribed mainly for LRTI or acute bronchitis cases.

Clinical response as assessed on the next follow-up visit conducted within a week were analyzed. Cough severity as assessed with Fisman’s scale documented significant improvement from the baseline visit (73.3%) in both the groups for Chronic (72%) and Acute cases (76%) respectively as highlighted in Figure 3.

Similarly, the wheezy symptom score associated with Lower respiratory tract infections (n=709, 82%) including Bronchitis showed significant improvement by 71.8%.

Safety Profile: Adverse events were noted in 46 cases (3.3%) and comprised mainly of tremor (1%), palpitation (0.9%), vomiting (0.7%). Most of these adverse events were mild and transient with none requiring treatment withdrawal or discontinuation of therapy. In two cases further treatment with nebulization and antibiotics was required. None of the cases reported any Serious adverse event or prolonged hospitalization.

Discussion

BCF containing fixed dose combination of Bronchodilator with mucolytics and/or expectorants are often prescribed for cough management. Review of literature highlights the clinical utility of these Bronchodilatory cough formulations in various respiratory tract conditions of acute or chronic cough especially with Terbutaline.

Levosalbutamol, the active stereoisomer of the racemic mixture, Salbutamol promises to offer a differentiated safety profile especially in terms of tremors, tachycardia or palpitations. The differential safety profile of Levosalbutamol is more likely to be highlighted during repeated administration of these Beta2 agonists especially for patients with chronic cough. The current study for the first time highlights this potential safety advantage for Levosalbutamol containing Bronchodilatory cough formulations for patients with acute or chronic cough. Pierson (1985) reported side effects including tremors (11%) amongst children administered salbutamol syrup formulation while in the current observational cohort, the same was noted in 14 cases (1%). These results seem to compliment the findings by Rai (2013) that reported higher patient satisfaction with Levosalbutamol than compared with Salbutamol (Racemic mixture, RAC). The 20-minute telephonic survey analysis showed, 92% caregivers administering LEV were “extremely” or “very satisfied” with therapy versus 51% administering RAC (p = 0.001).
dosing flexibility, and improved side effect profile of LEV were the sources of greatest satisfaction for parents/caregivers than RAC.5

In the current cohort analyses, the cough severity score assessed by FISMAN scale showed significant improvement by 72% for the chronic cases highlighting further the clinical role of Levosalbutamol containing bronchodilatory cough formulations in Bronchial asthma or cough variant asthma cases. In such cases the FISMAN scale for Cough Severity when combined with Cough frequency scores offers viable assessment strategies for Cough management especially in outpatient community settings and can positively correlate the differential clinical impact of the cough formulation during treatment period on the disease pathophysiology as compared with the conventional frequency score method.13

This analyses was observational in nature that evaluated the clinical utility and safety of Levosalbutamol containing Bronchodilatory cough formulation in outpatient centres involving community practice and needs to be further confirmed in a multicentric, randomized, clinical trials

Conclusion

Levosalbutamol containing bronchodilatory cough formulation remains a safe and effective option in the management of acute or chronic cough. Levosalbutamol offers better safety profile in terms of negligible incidence for gastrointestinal or central side effects compared to conventional racemic mixture of Salbutamol

Acknowledgements

BUS panel: Dr. N.P. Chhangani (Jaipur), Dr. Seeja Pradeep (Edapally), Dr. Ashwin (Shapur), Dr. Debasish Roy (Kolkata), Dr. Rashmi Bhurid (Mumbai), Dr. K. Prakash (Banglore), Dr. P.V. Shaji (Chennai), Dr. M.A. Raseed Khalidi (Hyderabad), Dr. Maria (UP), Dr. Raman (Ranipet), Dr. Umang Arora (Meerut), Dr. K.K. Singh (Mirzapur), Dr. Ashwin K Bhanushali (Mumbai), Dr. P.K. Mishra (Cuttack), Dr. Kirit J. Sisodiya (Surat), Dr. U. Narayan Swamy (Tenali), Dr. Manish Kumar Singh (Goa), Dr. Kundan Kumar (Purnea), Dr. Parag Gaikwad (Mumbai), Dr. Swapnil Usagoonkar (Goa), Dr. Muzeef Ahmed Jaragath (Bangalore), Dr. R.S. Bishen (Raipur), Dr. P. Satish (Bangalore), Dr. Sudhangshu Kumar Paul (Kolkata), Dr. S.N. Das (Ranaghat), Dr. A.S. Haldar (Midnapore), Dr. Faheem Md. Chesi (Srinagar), Dr. Kirit S. Mod (Ahmedabad), Dr. Harmohan Mohapatra (Bhubaneswar) Dr. D.J. Jagannath Swamy (Berhampur), Dr. Sanjib Kumar Chakraborty (West Bengal), Dr. Nasim A. (Patna), Dr. V.Shoba Rani (Tadepalligudem, AP), Dr. Bidyut Nath (Guwahati), Dr. R. Jayaraman (Chennai), Dr. Ashok K. Chakravarty (Delhi), Dr. Sanjeev Tandon (Delhi), Dr. K.S. Bohra (Dehradun), Dr. Some Suiva Bose (Kolkata), Dr. Vikram V. Mardhekar (Mumbai), Dr. Sachin Karnakar (Mumbai), Dr. Mita Mohanti (Darjeeling).

The authors would also like to acknowledge the services and support provided by Ms. Preeti Kumbhar, Ms. Nilofer Allarakha and Mr. Akshay Mahapatra for the statistical analyses and manuscript development.

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