ORIGINAL ARTICLE

Efficacy and Safety of Levocloperastine in the Treatment of Dry Cough: A Prospective Observational Study

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Abstract

Purpose/Aim: To evaluate effectiveness and safety of Levocloperastine in the treatment of dry cough in adult Indian patients.

Methods: In this prospective, observational study, patients aged 18-60 years, presenting with dry cough and prescribed with Levocloperastine at baseline or a day prior to enrolment, as per standard clinical practice, were recruited from 3 centers in India. The scores of cough severity (100 mm VAS), cough frequency since last 24 h (7-point Likert scale), sleep disruption due to night-time awakenings (10 cm VAS), quality of life (QoL) (Leicester Cough Questionnaire [LCQ]), and number of days for achieving minimal important difference (MID) in cough severity (17 mm improvement on VAS) were assessed from baseline to Day 14. In addition, physicians' assessment of effectiveness of Levocloperastine at Day 14, adverse drug reactions (ADRs) and proportion of patients reporting sedation and other central nervous system side effects were also reported during the study. Descriptive statistics was used to summarize the data.

Results: A total of 100 patients were enrolled in the study. The mean scores of cough severity, cough frequency and sleep disruption due to night-time awakening were significantly reduced from baseline to Day 14 ($p<0.0001$). A significant improvement in QoL scores (total and by domain) was noted from baseline to Day 14 ($p<0.0001$). Post treatment with Levocloperastine, the mean time for achieving MID was 5.3±0.26 days. Disappearance of cough was reported in 44% of patients; 54% patients reported improvement of cough by Day 14. No ADRs, cases of sedation or other side-effects were reported in the study.

Conclusion: Levocloperastine was found to be effective and safe in the management of dry cough. A significant reduction in severity scores, frequency of cough and sleep disruption was reported, with an overall improvement in patient's QoL.

Introduction

Cough is an innate defensive mechanism of the respiratory tract, which enables in clearing mucus, noxious substances, and infections from larynx, trachea and larger bronchi.[1] However, persistent cough may be annoying to the patient and sometimes considered as a warning sign of several diseases.[2] It is further recognized as one of the most common reasons for patients seeking medical treatment in hospital outpatient visits.[3] A dry cough, i.e. absence of phlegm on coughing, is normally caused due to sensitization of cough receptors, which in turn may be due to increased levels of inflammatory mediators (prostaglandins, bradykinin, histamine, leukotrienes), chemical irritants (aerosol sprays) or pollutants and bronchoconstriction. It interferes with normal breathing and results in disturbed sleep, loss of work days and weakness when lasts for >8 weeks.[4]

Dextromethorphan and codeine are the two most commonly preferred centrally acting antitussives in patients with dry cough.[4] However, due to side-effects like drowsiness, nausea, vomiting, dizziness, and dry mouth commonly reported with these antitussive agents, there is a therapeutic need for more effective and better tolerated antitussives.[5] Levocloperastine, the levorotatory isomer of DL-cloperastine, is a non-opioid antitussive agent with a rapid onset of action. It is very effective, safe and well tolerated in the treatment of cough associated with many acute and chronic conditions, owing to its dual mechanism of action on the central bulbar cough center and peripheral receptors in the tracheobronchial tree.[6] In 2004, Aliprandi et al reported Levocloperastine as an effective and well-tolerated alternative to DL-cloperastine, codeine, and Levodropropizine in the treatment of dry cough associated with varied respiratory conditions.[6] However, there is a paucity of published data on effectiveness and safety of Levocloperastine in the treatment of dry cough in Indian patients. Hence the current study was conducted to determine the patient-and physician-reported effectiveness and safety of Levocloperastine in the treatment of Indian patients with dry cough.

Methods

Patients

Patients presenting with dry cough and prescribed with Levocloperastine at baseline or a day prior to enrolment, as per standard clinical practice, were recruited in this study. These patients were enrolled over a period of approximately 2 months (November to December 2017) from 3 centres (one each at Karnataka, Delhi, and Maharashtra) in India. Patients aged 18-60 years and willing to provide their voluntary consent by signing

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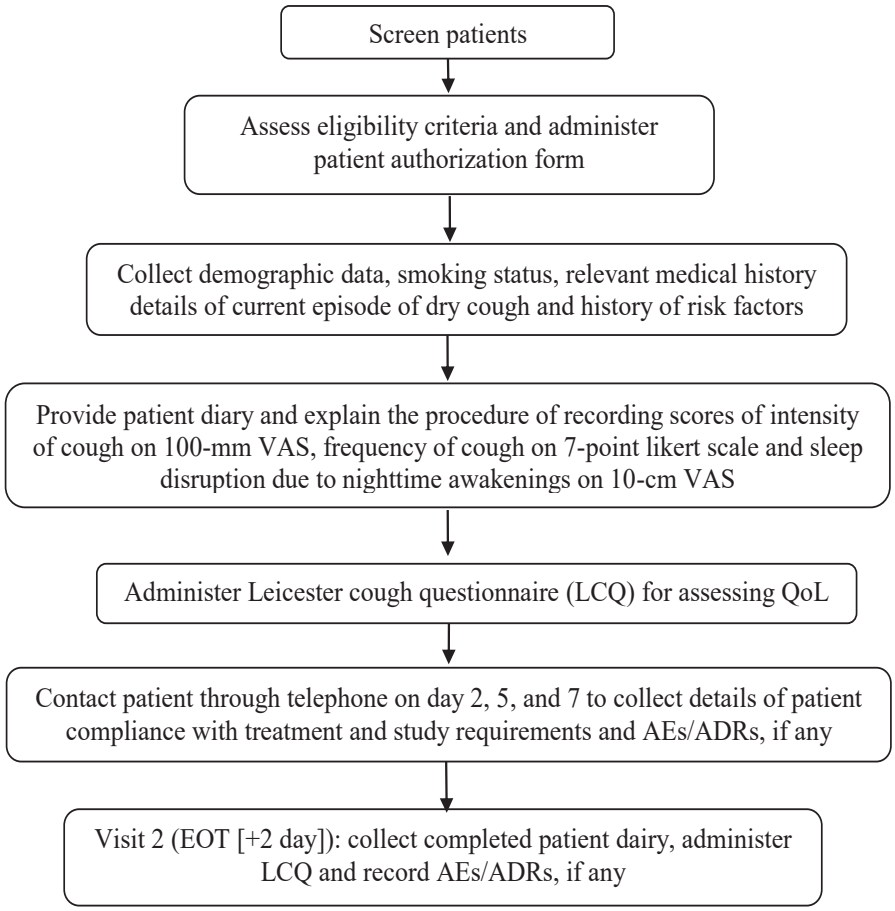


Fig. 1: Description of study activities

the patient authorization form were considered eligible to participate in the study. Pregnant and lactating women or patients unable to complete the patient diary were excluded from the study. The study protocol and other related documents were approved by the respective institutional ethics committees. The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice standards, Indian Council of Medical Research, Indian GCP guidelines and approved protocol.

Study design

This was a prospective, multicentric, observational study consisting of 2 visits (baseline visit and an end of treatment visit at Day 14 [+ 2 days]). Patients were followed up telephonically on Days 2, 5 and 7 of enrolment and the data regarding patient compliance with treatment, study requirements (daily completion of the patient diary) and adverse drug reactions (ADRs), if any, were collected (Figure 1).

Data collection

Patient demographics and anthropometric details, smoking status, medical history, history of risk factors associated with dry cough, vital parameters (systolic and diastolic blood pressure, pulse and respiratory rate and body temperature), physical examination findings, concomitant medication, laboratory investigations and ADRs were recorded. The details of current episode of dry cough, including date of onset, duration of cough, symptoms, and associated etiologies were collected. Based on the duration, cough was categorized as acute (<3 weeks), subacute (3-8 weeks), and chronic (>8 weeks). Patients' quality of life (QoL), severity and frequency of cough, and sleep disruption due to night-time awakenings were reported at baseline and Day 14.

Study Assessment Tools

The severity of cough was assessed on 100 mm visual analogue scale (VAS) where a score of 0 indicated "no cough" and a score of 100 as "worst cough ever".

The frequency of cough since last 24 h was recorded on a 7-point Likert scale. The score of 0 indicated "not at all", 1 "occasional", 2 "a little", 3 "somewhat", 4 "a lot", 5 "very much", and 6 "constant".

Sleep disruption due to night-time awakenings was rated on 10 cm VAS where a score of 0 indicated "best possible sleep" and 10 as "worst possible sleep".

The QoL was assessed using 19-item patient-reported Leicester Cough Questionnaire (LCQ). The LCQ comprises of three health domains: physical (Q1, 2, 3, 9, 10, 11, 14 and 15), psychological (Q4, 5, 6, 12, 13, 16 and 17) and social (Q7, 8, 18 and 19). Each item assesses symptoms or the impact of symptoms on a 7-point Likert scale. The domain score ranges from 1 to 7 and the total score ranges from 3 to 21. The total score was calculated by adding the domain scores together. The higher score indicates better QoL of a patient.

The investigator and/or designated personnel were responsible for LCQ administration. The daily rating of severity and frequency of cough and sleep disruption due to night-time awakenings were maintained in the patient diary.

Study outcomes

The primary outcome measure of interest was mean change in cough severity score from baseline to Day 14. The changes in cough frequency score, sleep disruption score based on night-time awakenings, and LCQ scores from baseline to Day 14 were the secondary outcome measures of importance. The other secondary outcomes of the study were time (in days) for achieving minimal important difference (MID) in cough severity (i.e., decrease in VAS of intensity of cough by 17 mm) and physician-reported effectiveness of treatment with Levocloperastine. The safety outcomes were nature and frequency of ADRs and the proportion of patients reporting sedation and other central nervous system side-effects (dizziness, drowsiness, drug dependence etc.) while on treatment with Levocloperastine.

Statistical analysis

Assuming 20% drop- out rate, the estimated number of enrollments in the study was 39 patients. However, since dry cough was a common clinical

Table 1: Baseline characteristics

Parameter	Total number of patients (N=100)
Age (years), mean±SD [range]	43.3±13.46 [18.0: 60.0]
Males: Females, n	57:43
Occupation, %	
Professional	9
Semi-Professional	10
Clerical, shop-owner, farmer	6
Skilled worker	10
Semi-skilled worker	12
Unskilled worker	11
Unemployed	42
Weight (kg), mean±SD [range]	63.9±12.43 [35.0: 85.0]
Height (m), mean±SD [range]	1.6±0.09 [1.4: 1.8]
Body mass index (kg/m^2), mean±SD [range]	24.8±4.36 [15.6: 35.8]
Smoking status, %	
Never	87
Ex-smoker (people who had quit smoking for at least 1 year)	3
Occasional smoker (1-2 cigarettes per week)	6
Current smoker (>1-2 cigarettes per week)	4
Cough severity score, mean±SD	69.2±14.43
Cough frequency score, mean±SD	3.4±1.31
Sleep disruption score, mean±SD	6.2±1.93
LCQ score, mean±SD	
Physical	4.9±1.00
Psychological	5.5±1.09
Social	5.7±1.18
Total score (physical+psychological+social)	16.1 ± 2.51

condition and multiple variables were assessed, the study recruited a total of 100 patients in this study; which was beyond the estimated sample size.

The descriptive statistics was used to analyze the study results; the continuous variables were presented as mean±standard deviation and the categorical variables as frequencies and percentages. All the three types of scores for acute, subacute and chronic cough at baseline were compared with the scores at Day 14 using paired *t*-tests, at 5% level of significance. The time (in days) for achieving MID was presented through Kaplan-Meier estimates. All the data were analyzed using SAS version 9.3.

Results

Patient Demographics

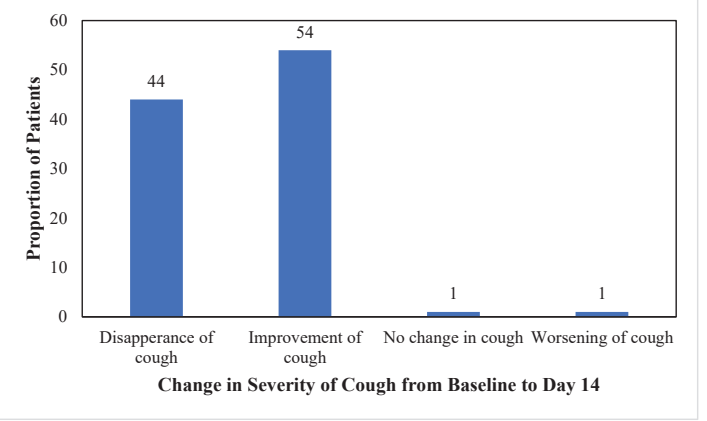
Out of 100 enrolled patients, 57% were males, 42% were unemployed, and 87% were non-smokers. The mean age and body mass index of the overall population was 43.3 ± 13.46 years and 24.8 ± 4.36 kg/m^2, respectively.

A total of 40%, 28% and 32% of patients had an acute, subacute and chronic cough, respectively. The most common causes associated with dry cough were exposure to environmental irritants (66% patients), allergy (61% patients), asthma (46% patients), and respiratory tract infection (22% patients). More than 20% of patients had the symptoms of nasal discharge (66% patients), wheezing and shortness of breath (58% patients), tiredness (25% patients), and frequent throat clearing (21% patients) (Table 1). Of the commonly used concomitant medications, salbutamol (40%), budesonide (14%), and formoterol (12%) were more predominant.

Table 2: Analysis of study variables

Parameters	Acute (n=40)	Subacute (n=28)	Chronic (n=32)	Total number of patients (N=100)
Change in severity of cough from baseline to Day 14 (100 mm VAS scale), mean±SD	-53.9 ±19.8*	-56.8 ±20.0*	-56.3±15.7*	-55.5±18.5*
Time (days) for achieving minimal important difference				
Number of censored:uncensored events	3:37	1:27	0:32	4:96
Mean±SE [median]	5.3±0.47 [4.0]	5.4±0.52 [5.0]	5.3±0.39 [5.0]	5.3±0.26 [5.0]
Change in frequency of cough from baseline to Day 14 (7-point Likert scale), mean±SD	-2.4±1.58*	-2.5±1.67*	-2.3±1.46*	-2.4±1.56*
Change in sleep disruption from baseline to Day 14 (10 cm VAS scale), mean±SD	-5.1±2.08*	-4.6±2.54*	-5.3±1.59*	-5.0±2.08*
Change in LCQ score from baseline to Day 14, mean±SD				
Physical	1.4±1.03*	1.6±1.05*	2.4±1.06*	1.7±1.12*
Psychological	1.1±0.88*	1.1±1.12*	1.6±1.29*	1.2±1.11*
Social	0.9±1.23*	0.9±1.07*	1.3±1.30*	1.0±1.21*
Total score (physical + psychological + social)	3.4±2.35*	3.6±2.56*	5.2±2.85*	4.0±2.68*

*p<0.0001; paired t-test



Disappearance of cough: If the score of severity of cough on 100 mm VAS scale was zero at Day 14.
Improvement of cough: If the score of severity of cough on 100 mm VAS scale reduced at Day 14 from baseline.
No change in cough: If the score of severity of cough on 100 mm VAS scale was same at baseline and Day 14.
Worsening of cough: If the score of severity of cough on 100 mm VAS scale increased at Day 14 from baseline.

Fig. 2: Physician assessment of effectiveness of levocloperastine

Patient-reported effectiveness of Levocloperastine

There was an improvement in all the clinical symptoms after 14-day Levocloperastine treatment compared with the baseline values. The mean score for severity of cough significantly declined from baseline (69.2±14.43 mm) to Day 14 (13.7±17.21 mm, p<0.0001). Similar results were reported when cough frequency and sleep disruption scores were compared at Day 14 against the baseline values (cough frequency: 3.4±1.31 to 1.0±1.16; sleep disruption: 6.2±1.93 cm to 1.2±1.59 cm, p<0.0001). The mean time for achieving MID was 5.3±0.26 days. A statistically significant improvement was noted in mean LCQ score (total and by domain) over the period of 14 days (p<0.0001). Similar results were observed when the data was analyzed based on the duration

of cough (acute, subacute and chronic cough) (Table 2).

Physician-reported effectiveness of Levocloperastine

Physicians reported an improvement in the severity of cough in 54% of the patients and disappearance of cough in 44% of the patients at Day 14 (Figure 2).

Safety

No ADRs, sedation or other central nervous system side-effects were observed in patients post treatment with Levocloperastine. No significant changes in vital parameters, spirometry parameters (FEV1, FVC, FEF25%-75%, and PEFR) or physical findings were reported during the course of study.

Discussion

Dry cough is a frequent problem reported in clinical practice due to its high association with numerous etiologies.[7] An increase in the severity and frequency of dry cough is often annoying to patients and causes sleep disruption due to night-time awakening. This eventually imposes a substantial impact on their QoL, loss of productivity, and may lead to an increased economic burden.[8] Hence, an adequate management of dry cough using antitussive agents is highly warranted. Of all antitussive agents, codeine and dextromethorphan are usually preferred for the treatment of dry cough by physicians. However, these cough suppressants usually result in AEs like nausea, drowsiness, dry mouth, etc, which further limits their use.[9] Levocloperastine, a nonopioid antitussive, peripherally inhibits the release of inflammatory mediators and reduces bronchospasm, which explicates its high efficacy and tolerability in cough across many chronic and acute respiratory indications.[6] In the present prospective, observational study, we reported the effectiveness and safety of Levocloperastine in the treatment of Indian patients with dry cough.

In this study, a significant reduction in the severity and frequency of cough and sleep disruption was reported post treatment with Levocloperastine for 14 days. In addition, the estimated time to achieve MID was 5.3 days, reflecting high antitussive effect of Levocloperastine. Similar results were reported when dry cough was categorized by its duration. Levocloperastine treatment was found to have a similar improvement in respiratory symptoms across cases of acute, subacute, and chronic dry cough; thereby providing a therapeutic effectiveness of Levocloperastine, irrespective of cough duration. Physicians also reported an improvement and disappearance in the severity of cough in 54% and 44% of the patients, respectively after 14-day treatment. Similar results, in terms of significant improvement in cough symptoms (both intensity and frequency of cough) with Levocloperastine, were reported in 9 controlled clinical trials (analyzed by Aliprandi et al 2002) conducted in adult patients involving a total of 650 patients.[10]

Dry cough causes a significant impact on patient's QoL, affecting their physical, psychosocial, and social aspects of life.[4,11] In this study, the authors have used LCQ, a brief, simple and validated cough-related health status questionnaire to assess the effect of Levocloperastine treatment. LCQ was chosen based on the internal reliability, repeatability, and responsiveness, as reported in other studies.[12] In this study, treatment with Levocloperastine was found to significantly improve the physical, psychosocial and social scores, and the overall QoL of the patient. This could be attributed to the dual mechanism of action (central and peripheral) of Levocloperastine, which in turn aided in improving the respiratory symptoms and the overall QoL of the patient.

There was no reported evidence of central AEs like sedation, addiction or dependency or interference with cardiological and gastrointestinal function with the use of Levocloperastine, indicating favorable safety and tolerability profile of the drug.[13,14] The dual mechanism of action along with distinct stereoisomeric configuration (levoisomer) further explains the safety and tolerability profile of Levocloperastine. In line with the published literature, none of our patients reported sedation or other central nervous system side-effects.

Levocloperastine, along with its unique pharmacodynamic profile did not interact with other drugs, which made it a safe alternative for patients who take concomitant medications for their underlying conditions.[10] The commonly used concomitant medications in our study were salbutamol (40%), budesonide (14%), and formoterol (12%).

The common causes of dry cough include viral or bacterial infections, asthma, allergies, air pollutants, cigarette smoking and side-effects of medications. In our study, more than 40% of the patients reported the causes of dry cough as environmental factors (66%), allergy (61%) or asthma (46%). Generally, dry cough occurs in association with other symptoms, which varies from indication-to-indication. The frequently reported symptoms that occur along with dry cough are fatigue, fever, sore throat, headache, body ache, hoarse voice, nausea and vomiting, runny nose, and wheezing. The serious symptoms that are reported along with dry cough are shortness of breath, difficulty in speaking, frequent urination, rapid heartbeat and severe pain upon swallowing.[8] In this study, more than 20% of the patients reported the symptoms of nasal discharge (66%), wheezing and shortness of breath (58%), tiredness (25%), and frequent throat clearing (21%).

Our study has few strengths and limitations. This is the first of its kind study to assess the effectiveness and safety of Levocloperastine in the treatment of dry cough in Indian patients with medical history of respiratory, circulatory, and endocrine, nutritional and metabolic diseases. The number of patients enrolled in the study was much above the optimal number calculated statistically. Further, all the scales used in this study for assessments are validated and widely used, ensuring the credibility of our findings. Another strength of this study was that the effectiveness of Levocloperastine in the treatment of dry cough was studied by duration of cough i.e. across acute, sub-acute, and chronic dry cough cases. Moreover, in this study, the patient-reported responses were validated by physicians' assessment about the treatment. However, the study has few limitations. Firstly, this was a non-comparative study, limiting the viability of our results. Secondly, no subgroup analysis was done, which could restrict the interpretation of our results in patients with different duration of cough, gender, and different age categories. Thirdly, Levocloperastine treatment was at the discretion of the physician; hence no fixed dosage of Levocloperastine was

provided to the patients which again restricted the feasibility of our results. Fourth, we did not have intermediate study visits between baseline and Day 14 to record the effectiveness and safety of Levocloperastine treatment. Therefore, one cannot rule out the possibility of natural recovery in the study. Lastly, it was not a Pan-India study, which restricted the interpretation of our results across the population of different geographical areas. Nevertheless, this study was the first attempt to explore the benefits of Levocloperastine among patients and healthcare practitioners for the management of dry cough in India.

Conclusion

Levocloperastine was found to be effective, safe, and well-tolerated in the treatment of dry cough in Indian adult patients. This non-opioid, antitussive, significantly reduced the severity and frequency of cough along with sleep disruption caused as the result of night-time awakenings. Significant improvement in all domains (physical, psychological, and social) of patient's QoL was evident. There was no evidence of ADRs, sedation, and other central nervous system side-effects, which suggests Levocloperastine to be a better alternative to other antitussives in the clinical management of dry cough. However, comparative studies are warranted to further confirm the effects of Levocloperastine across different clinical conditions.

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Conflict of Interest

Dr. Deepa Sholapuri authored this article in the capacity as an employee of Abbott Healthcare Pvt. Limited. All other authors have declared and confirmed that there is no conflict of interest with respect to the authored article.

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