JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 35, no. 4, 1377-1381 (2021)

LETTER TO THE EDITOR

Levodropropizine in children: over thirty years of clinical experience

G. Ciprandi[1], A. Licari[2], M.A. Tosca[3] and G.L. Marseglia[2]

[1]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy; [2]Pediatric Clinic, Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [3]Pediatric Allergy Center, Istituto Giannina Gaslini, Genoa, Italy

Received April 15, 2021 – Accepted July 26, 2021

To the Editor,

Under normal conditions cough is a protective reflex with two main purposes: to clear excessive secretions and mucous from the large airways, and to prevent foreign material from entering the lower airways. The cough reflex is triggered by stimulation of receptors on vagal afferent nerves ending in the larynx, trachea and bronchi. these stimuli trigger sensory nerve fibres in the respiratory tract, including C-fibres and mechanically sensitive Aδ-fibres, and reach the neural cells normally dedicated to the generation of the breathing pattern. However, cough can sometimes become excessive and potentially harmful to the airway mucosa, in fact, it is one of the most common reason why individuals seek a medical consultation in primary health.

Acute cough lasts less than four weeks. An acute cough is commonly associated with upper respiratory tract infection (URTI), which is usually of viral origin so that it is called post-viral cough. Consistently, acute cough due to URTI is the most common reason for primary care worldwide. It is generally self-resolving, but may be very bothersome for a child, but overall, for the family.

Chronic cough (lasting more than 8 weeks) can be caused by several lung disorders such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer, or extra-pulmonary disorders such as gastro-esophageal reflux disease. In children, differently from adults, the etiology of coughing is often related to viral URTI, prolonged bacterial bronchitis and asthma. As a result, antitussive treatments are commonly used in clinical practice. However, cough control is a challenge as there is a need to identify an antitussive medication that has to be effective and above all safe in children.

There are two classes of antitussive agents available for the treatment of cough in children: central action cough suppressants (e.g. codeine, dextromethorphan and cloperastin), and peripheral action antitussive agents (such as levodropropizine). The efficacy and safety of most over-the-counter (OTC) symptomatic antitussive drugs has recently been questioned, because centrally acting antitussive drugs have shown poor tolerability related to side effects on the central nervous system.

In the last five years, several studies and surveys, carried out by Regulatory Authorities and Scientific Societies, reported that cough negatively impacts quality of life, but for most patients their cough medications have limited or no effectiveness. Thus, the safety of such drugs, particularly when they are being administered to paediatric populations and patients with respiratory disorders, is very important.

There is therefore a clear need for safe and effective drugs for cough treatment, especially in

Key words: children; cough; levodropropizine; respiratory infections

Corresponding Author:
Giorgio Ciprandi,
Via P. Boselli 5,
16146, Genoa, Italy
e-mail: gio.cip@libero.it

0393-974X (2021)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

children. Levodropropizine (LDP) is a non-opioid peripheral antitussive drug that is therefore devoid of effects on the central nervous system. LDP is indicated for adults and children over 2 years of age for the symptomatic therapy of cough (1).

The current paper presents the literature concerning LDP treatment in children with cough, analyzing its efficacy and tolerability profile and its use in clinical practice in the paediatric population,

Levodropropizine

LDP (S(-)-3-(4-phenyl-piperazin-1-yl)-propane-1,2-diol) is the levorotatory isomer of dropropizine, a piperazine derivative. LDP is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations between 40 and 60 minutes after oral administration, and is also rapidly distributed throughout the body (1). In addition, it has a plasma half-life of approximately 1.5 to 3 hours and has linear pharmacokinetics over a concentration range of 30, 60 and 90 mg in healthy volunteers (1). This enantiomer has an antitussive effect comparable to dropropizine racemic drug, but with the advantage of causing fewer adverse effects, mainly related to the central nervous system (12). Its peripheral antitussive action is due to the inhibition of vagal C fiber activation. Several studies on animal models and on humans support the thesis of the lack of centralized action. Gunella and colleagues conducted a controlled study *versus* placebo to evaluate the effects of 60 mg levodropropizine t.i.d. for four days on the respiratory center in 40 hypercapnic and hypoxiemic patients. Findings in the two treatment groups were similar, confirming the absence of effect at the central level of levodropropizine (1).

Recently, a single-blind crossover study was carried out on patients with chronic cough of different origin to investigate the effect of levodropropizine (60 mg), or dihydrocodeine (15 mg), or placebo on the respiratory response to a standard CO2 re-breathing testing. The results showed that, unlike dihydrocodeine, both levodropropizine and placebo did not significantly affect respiratory response to hypercapnia, supporting the peripheral action of levodropropizine (2).

Since the launch, more than 30 years ago, the antitussive activity of LDP has been extensively studied and the drug has been proven to be effective and safe in patients of all ages (3,4). In particular for pediatric age, many clinical studies, including meta-analysis, have confirmed the antitussive efficacy and tolerability of LDP for the treatment of acute and chronic cough in children (5, 6).

The evidence in children

The research included published studies cited in PubMed (the search included the term "levodropropizine in children"). In 1989, three studies investigated the efficacy of LDP in children with ages ranging between the first month of life and 12 years, who were suffering from several respiratory diseases, including acute bronchitis, asthma, bronchopneumonia, tracheitis. The efficacy was assessed in terms of reducing the intensity and frequency of coughing after treatment and tolerability as absence of adverse events.

In the first published study, Fiocchi and colleagues enrolled 70 children (mean age 4.5 years, 31 males) and administered LDP oral drop formulation at 2 mg/Kg/day for five days. LDP was effective in 69/70 children and cough scores significantly ($p<0.01$) diminished. In no case was there any early interruption of treatment, and somnolence was reported in 3 (4.28%) children (7). The second study, carried out by Cogo and colleagues, was a multicenter study with 172 children aged between 1 and 12 years, out of a total sample of 1,304 patients (mean age 4.6 years), who had acute cough due to upper tract respiratory infection. 3-6 mg/kg t.i.d. of LDP oral drops were administered for 7 days. The effectiveness of the treatment was judged by doctors to be good in 93% of cases, having found a reduction or absence of the cough symptom, while tolerability was considered good in 98% of cases. Patients and parents of the children reported that the improvement in coughing occurred during the first 3-4 days of therapy. The last of the three studies, was another multicenter study only, focused on a wide range of pediatric respiratory diseases. A total of 180 children, age between 5 months and 12 years, were enrolled and treated with 1-2 oral drops/kg die of LDP for 7 days. The clinical judgment on

the efficacy of LDP was good in 94% of cases, and tolerability was good with only 3% of cases judged unsatisfactory, probably due to the simultaneous presence of antibiotic therapy which makes it difficult to attribute responsibility.

Two comparative double-blind, randomized clinical trials evaluated antitussive efficacy and tolerability of levodropropizine *versus* dropropizina and dextromethorphan in children. Banderali and colleagues compared LDP (2mg/kg) *vs* dropropizine (1mg/kg) 3 times a day for 3 days in 258 children (aged between 2 and 14 years) with dry cough. The results showed that both treatments were significantly ($p<0.001$) effective in reducing cough, but LDP was better tolerated. Sleepiness was found to be twice as frequent in the dropropizin group compared to the LDP group (10.3% *vs* 5.3%) (8). Instead, Kim Doon Soo and colleagues, compared LDP syrup *vs* dextromethorphan, one of the major central antitussive drugs, in 77 pediatric patients (aged between 2 and 3 years) with non-recurrent or slightly recurrent coughs accompanied by acute chronic bronchitis. The severity and frequency of cough were more significantly reduced after 2-3 days in the LDP group than in the dextromethorphan group ($p=0.003$). In conclusion, LDP has a more favourable antitussive efficacy and benefit profile than dextromethorphan.

De Blasio and colleagues reviewed cough management from a practical point of view. The review identified that among the drugs used for the symptomatic treatment of cough, peripheral-acting antitussive drugs, such as LDP, showed higher effectiveness in relieving cough, mainly in childhood. Moreover, all these studies provided evidence that LDP was more tolerated than central antitussive drugs (9). Consequently, the same authors analyzed the efficacy of LDP in pediatric cough, highlighting the concept that the cough morbidity extends to parents, other family members, caregivers, and teachers. The most common medications used to relieve acute cough in children have clinically relevant sedative effects because they are narcotics or first-generation antihistamines. On the contrary, LDP, being a peripheral antitussive agent, is substantially devoid of adverse effects on the central nervous system (10).

Furthermore, these authors carried out a pediatric observational study evaluating children with acute cough associated with URTI. This study investigated cough epidemiology and its impact on the quality of sleeping and children's daily activities, but also on their parents. The results reported that cough significantly affected sleep. A total of 433 children (mean age 6.1 years) were enrolled and divided into 3 treatment groups: 101 children were treated with LDP, 60 with central antitussive agents (cloperastine or codeine), and 80 without any active drug for six days. The results showed a cough resolution was significantly higher with levodropropizine than with central antitussives (47% *vs* 28% respectively, $p = 0.0012$) or no therapy, independent of antibiotic use or concomitant illnesses (11).

Zanasi and colleagues provided a meta-analysis of LDP in the treatment of cough in adults and children. This meta-analysis evaluated seven clinical studies, including 1,178 patients, to compare LDP with control treatments (codeine, cloperastine, dextromethorphan). The analysis showed that LDP was an effective antitussive ($p = 0.0015$) drug in both pediatric and adult populations, as it induced a more significantly reduced cough intensity and frequency, as well as nocturnal awakenings in comparison with central antitussive drugs (6).

The same authors carried out a prospective observational study to evaluate 330 children with acute post-viral cough. The treatment lasted six days. Children were subdivided in four groups: the first group (123 children) was treated with antitussive medications, including central antitussive agents (44 children) and peripheral ones (79 children). The second group was treated with antibiotics alone (89 children). The third group took antitussive agents combined with antibiotics. The last group was without active treatment (80 children). Severity, frequency, and type of cough were assessed at baseline and the end of the study. Antitussive drugs were more effective than antibiotics. Moreover, considering peripheral antitussives, the resolution of cough was significantly higher with antitussives than with antibiotics ($p < 0.01$). Therefore, the authors concluded that antibiotics are not indicated

to treat acute cough due to URTI, whereas peripheral antitussive drugs should be the treatment option.

Recently, an international group of experts specialized in cough management met to discuss and increase their knowledge on the cough mechanism and the activity of LDP as a peripherally acting antitussive drug (1). The authors analyzed the studies in the last thirty years conducted on adults and children with a cough. They concluded that LDP trials showed a documented efficacy in cough control, associated with no evident central depressant activity.

Development of new cough treatments still remains a challenge, as even the latest available pharmacological approaches are still unsafe and ineffective. Therefore, the authors suggest that, at the present time, LDP is an important therapy for the treatment of different types of cough, especially in children, thanks to its very good efficacy and safety profile (1).

CONCLUSION

Cough is one of the most frequent symptoms and is consequently the most common reason for a medical visit. Cough is a very bothersome symptom and significantly affects the quality of life of both the child and the parents (12). Therefore, even though the acute post-viral cough is self-resolving, there is a need to relieve it. The majority of antitussive medications act on the central nervous system and consequently have relevant side effects. In this regard, LDP acting peripherally represents an important therapeutic option. LDP exerts its activity on the sensory fibers, namely the C-fibers, involved in the genesis of cough. In animal models, it was demonstrated that levodropropizine could act on C-fibers. Clinical studies on humans confirmed its peripheral action.

In conclusion, all these results support the favorable benefit/risk profile of LDP in the management of cough. At present, LDP seems to be an antitussive drug of first choice that acts on peripherical mechanisms of the cough reflex and is devoid of central adverse events, contrary to the common centrally-acting antitussives. The clinical experience highlights that LDP is effective and safe in children with cough.

CONFLICT OF INTEREST: Each author declares that he/she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement) that might pose a conflict of interest in connection with the submitted article. Dompé Italia gave an unrestricted grant to pay the publication fees.

REFERENCES

1. Birring S, De Blasio F, Dicpinigaitis PV, et al. Antitussive therapy: a role for levodropropizine. Pulm Pharmacol Therap 2019; 56:79-85.
2. Mannini C, Lavorini F, Zanasi A, Saibene F, Lanata L, Fontana G. A randomized clinical trial comparing the effects of antitussive agents on respiratory center output in patients with chronic cough. Chest 2017; 151(6):1288-94.
3. Catena E, Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough. Comparison with dextromethorphan. Pulm Pharmacol Therapeut 1997; 2:89-96.
4. Fiocchi A, Arancio R, Murgo P, Banderali G. Levodropropizine effectiveness on nocturnal cough in asthmatic children. Eur Respir J 1991; 4:594.
5. De Blasio F, Dicpinigaitis PV, De Danieli G, Lanata L, Zanasi A. Efficacy of levodropropizine in pediatric cough. Pulm Pharmacol Therap 2012; 25:337-42.
6. Zanasi A, Lanata L, Fontana G, Saibene F, Dicpinigaitis PV, De Blasio F. Levodropropizine for Treating Cough in Adult and Children: a Meta-Analysis of Published Studies. Multidiscipl Respir Med 2015; 10:19.
7. Fiocchi A, Zuccotti GV, Vignati B, Pogliani L, Sala M, Riva E. Evaluation of the treatment with levodropropizine of respiratory diseases in children. Pediatr Med Chir 1989; 11:519-22.
8. Banderali G, Riva E, Fiocchi A, Cordaro CI, Giovannini M. Efficacy and tolerability of levodropropizine and dropropizine in children with non-productive cough. J Intern Med Res 1995; 23:175-8.
9. De Blasio F, Virchow JC, Polverino M, et al. Cough management: a practical approach. Cough 2011; 10:7.
10. De Blasio F, Dicpinigaitis PV, Rubin BK, De Danieli G, Lanata L, Zanasi A. An observational study on cough in children: epidemiology, impact on quality of sleep and treatment outcome. Cough 2012; 8:1.

11. Irwin RS. Introduction to the diagnosis and management of cough. ACCP evidence-based clinical practice guidelines. Chest 2006; 129:25S–27S.

12. Barnes PJ. The problem of cough and development of novel antitussives. Pulm Pharmacol Therapeut 2007; 20:416-22.