Review

Efficacy of levodropropizine in the pediatric setting: a meta-analysis of published studies

Summary
Cough in children is among the most common symptoms and may have a deep impact on children's and parents' sleep and quality of life, thus often requiring an empiric treatment with antitussive agents. Levodropropizine is a very well tolerated peripheral drug, while central cough suppressants (opioids and non opioids) may be associated with side effects that limit their use especially in children. After comprehensive literature search, a meta-analysis of 4 clinical studies of levodropropizine vs. control, including a total of 780 patients, was performed with the aim to evaluate the overall comparative efficacy of levodropropizine in the pediatric population. Meta-analysis of all standardized efficacy parameters (cough frequency, severity, and night awakenings) showed a highly statistically significant difference in the overall antitussive efficacy in favor of levodropropizine vs. control treatments (p=0.0044). The heterogeneity test for the efficacy outcome was not statistically significant (p=0.0856). Our meta-analysis indicates that levodropropizine is an effective antitussive drug in children, with statistically significant better overall efficacy outcomes vs. central antitussives (codeine, cloperastine, dextromethorphan), in terms of reducing cough intensity, frequency and nocturnal awakenings. These results further reinforce the favorable benefit/risk profile of levodropropizine in the management of cough in the pediatric setting.

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Introduction

Cough in children is among the most common problems referred to pediatricians, and occurs more frequently in preschool than in older children[1,2].
The etiology and management approach for cough in children differs greatly to that in adults, so the empirical approach commonly used in adults is unsuitable for children[3]. Clinical evaluation of cough in children should include an assessment of environmental factors, particularly tobacco smoke, parental concerns and expectations[4].
Most children with acute cough are likely to have an uncomplicated viral acute upper respiratory tract infection (URTI), but the possibility of a more serious problem, especially aspiration of foreign material, should always be considered[2,4].
Cough resulting from URTI, although usually self-limiting within 7 to 15 days, may be a distressing symptom that causes significant anxiety to parents for its frequency and severity. Cough may have a deep impact on the sleep of both children and parents, on the children's scholastic and sport activities and thus on their quality of life[4,5].
Therefore, an empiric treatment with antitussive agents is often used in pediatric cough, even though the administration of inappropriate or unnecessary medications for cough may be associated with side effects[1,6].
Mainly two classes of antitussive drugs are available for the treatment of cough in children: centrally acting (opioids and non opioids) cough suppressants, and peripherally acting antitussives. Codeine, dextromethor-

phan and cloperastine are among the most common centrally acting agents that are believed to inhibit cough primarily by their effect on the cough center, while levodropropizine is an orally administered non-opioid agent exerting peripheral antitussive action that results from inhibition of the cough reflex at the peripheral nerve level (sensory C fibres) with modulation of sensory neuropeptides within the respiratory tract[7-9].

In recent years, much attention has been drawn to the fact that some antitussive agents commonly used in the pediatric population are not supported by adequate efficacy data, especially in light of potentially associated side effects[1]. Centrally acting cough suppressants, although largely used, have no consistent evidence of efficacy and there are increasing reports of association with serious adverse events in children[3].

Methods

A comprehensive systematic literature search was performed on the main electronic databases (PubMed/MEDLINE, EMBASE, and Cochrane Library) from their inception throughout January 2012, to identify original clinical studies of levodropropizine for the treatment of cough in the pediatric population.

The inclusion criteria used to select studies were established *a priori*. Only controlled studies (vs. both active control and placebo) including pediatric patients and assessing efficacy endpoints related to cough outcomes were selected for our analysis. Non controlled studies and studies evaluating only safety endpoints were excluded.

A meta-analysis of studies meeting eligibility criteria was performed with the aim to evaluate the overall efficacy of levodropropizine versus control in children. Due to the small number of clinical trials in the pediatric population and considering their different clinical endpoints, the efficacy variables of the selected studies were standardized in order to allow comparison of the overall efficacy of levodropropizine versus control groups. Our meta-analysis was performed after standardization on the overall efficacy variables assessed as endpoints in the eligible studies (i.e., reduction in cough frequency, cough severity, and night awakenings). For each study, original Absolute Mean Delta were calculated as the mean differences between the baseline and final values of efficacy parameters in levodropropizine and control groups, with the respective (approximate) standard deviations (SD) and the number of cases (N) studied in single treatment groups. Standardized Mean Delta were calculated by means of the original Absolute Mean Delta (with their SD and N) and represent a fraction or multiple of unitary standard deviations, expressed as standardized units[10-12].

Study Selection

A total of 9 published clinical studies conducted with levodropropizine in the pediatric setting were identified by means of our systematic literature search, involving an overall population of 1242 children.

Out of these, 4 studies including a total of 780 patients met the eligibility criteria and were selected for our meta-analysis. Three studies of levodropropizine were performed vs. central antitussives (Banderali 1995[13], Kim 2002[14], and De Blasio 2012[7]), while one study was performed vs. placebo (Fiocchi 1991[15]).

The study of De Blasio et al.[7] evaluated the use of antitussive drugs in 433 children who required medical consultation for acute cough. A subgroup of 161 children received antitussive treatment with levodropropizine (N = 101) or central cough suppressants (codeine or cloperastine, N = 60). Both peripheral and central antitussives were effective in reducing the frequency and intensity of cough. However, a significant advantage was observed for levodropropizine vs. central drugs in terms of higher cough resolution ($p = 0.0012$) and lower unsuccessful treatment. The superiority of the peripheral antitussive levodropropizine vs. central drugs in terms of cough resolution was independent from cough severity, with statistically significant difference also in the subgroups of patients with higher cough intensity (moderate and severe).

In a double blind randomized study carried out by Kim et al.[14], the efficacy of levodropropizine was compared to the central antitussive dextromethorphan in 77 children with bronchitis. After 2-3 days of administration, both severity and frequency of cough were reduced more significantly in the levodropropizine group than in the dextromethorphan group ($p = 0.003$). Also the final efficacy score resulted significantly higher with levodropropizine vs. dextromethorphan ($p = 0.003$), showing a more favorable antitussive effectiveness of levodropropizine in comparison to dextromethorphan.

Banderali et al.[13] evaluated in a

double blind randomized study the efficacy of levodropropizine compared to dropropizine in the management of non-productive cough in 258 pediatric patients. The results demonstrated statistically significant decreases in the frequency of coughing spells and nocturnal awakenings with both levodropropizine and dropropizine, without significant difference between treatment groups.

The efficacy of levodropropizine vs. placebo on nocturnal cough was investigated by Fiocchi et al.[15] in a small double blind randomized study in 12 children with asthma. The number of nocturnal awakenings was significantly reduced with levodropropizine ($p = 0.008$) but not with placebo ($p = 0.159$).

The main characteristics of published studies evaluating the antitussive efficacy of levodropropizine vs. control in the pediatric setting are summarized in Table 1.

Main efficacy outcomes of the 4 clinical trials included in this meta-analysis were frequency of cough, severity of cough, and nocturnal awakenings.

Other 5 published open-label uncontrolled studies evaluating the antitussive effect and tolerability of levodropropizine in children, involving a total of 462 children, were excluded from our analysis according to selection criteria[16-20].

Results

Table 2 shows the original Absolute Mean Delta (with SD and N) calculated for each efficacy parameter (cough frequency, cough severity, and night awakenings) assessed in each of the eligible clinical studies, both in levodropropizine and control groups.

The results of the standardization of different efficacy variables, in order to make the efficacy parameters comparable, are also shown in Table 2 as Standardized Mean Delta (with 95% C.I. and p values between treatment groups).

The results of the meta-analysis of all standardized parameters, representing overall antitussive efficacy, showed a highly statistically significant difference in efficacy in favor of levodropropizine versus control treatments (including central cough suppressants), with a p-value of 0.0044 (Table 3).

The size of antitussive effect of levodropropizine vs. control treatments in the pediatric setting

Table 1. Clinical Studies of Levodropropizine vs. Control in Children.

Study	Sample Size	Age	Design	Condition	Results
De Blasio 2012[7]	433 children	1-15 yrs	Levodropropizine vs. Cloperastine/ Codeine	URTI-related Cough	Significantly higher cough resolution (p=0.0012) and lower unsuccessful treatment with levodropropizine, independently from cough intensity.
Kim 2002[14]	77 children	2-3 yrs	Double blind randomized Levodropropizine vs. Dextromethorphan	Bronchitis Cough	Significantly higher reduction in cough severity and frequency with levodropropizine (p=0.003).
Banderali 1995[13]	258 children	2-14 yrs	Double blind randomized Levodropropizine vs. Dropropizine	Non-Productive Cough	Significant decrease in cough frequency and night awakenings with both levodropropizine and dropropizine.
Fiocchi 1991[15]	12 children	2-8 yrs	Double blind randomized Levodropropizine vs. Placebo	Asthmatic Cough	Significant reduction in nocturnal awakenings with levodropropizine (p=0.008), not with placebo.

Table 2. Absolute and Standardized Mean Delta (lLevodropropizine vs. Controls).

Studies/ Parameters	Levodropropizine			Controls			Standardized Mean Delta	95% C.I.		p
	Absolute Mean Delta	SD	N	Absolute Mean Delta	SD	N		Lower	Upper	
Banderali 1995[8]/ Frequency	-8.4	17.3	130	-7.7	13.7	126	-0.045	-0.291	0.202	0.7216
Kim 2002[14]/ Frequency	-1.3	1.14	38	-0.7	1.12	37	-0.525	-0.996	-0.055	0.0290
Banderali 1995[8]/ Nocturnal awakenings	-1.0	2.55	132	-1	2.46	126	0.000	-0.246	0.246	1.0000
Fiocchi 1991[15]/ Nocturnal awakenings	-1.06	0.81	12	-0.46	0.74	12	-0.747	-1.639	0.146	0.0966
Kim 2002[14]/ Severity	-1.2	1.0	38	-0.7	0.99	37	-0.495	-0.967	-0.028	0.0391
De Blasio 2012[7]/ Severity	-1.58	0.96	101	-1.1	1.13	60	-0.465	-0.792	-0.139	0.0055

Differences indicate improvement in efficacy parameters

is shown in the overall efficacy meta-analysis chart (Figure 1). Concerning the estimated efficacy outcomes, levodropropizine was superior to controls in all 4 clinical studies, also reaching a statistically significant difference ($p < 0.05$) in 2 studies[1,14].

In our meta-analysis, the test of heterogeneity for the efficacy outcome was not statistically significant ($p = 0.0856$).

Discussion and Conclusions

Cough is very common in children of all ages and its frequency and severity may have a deep impact on children's and parents' sleep and quality of life, therefore often requiring an empiric treatment with antitussive agents[7].

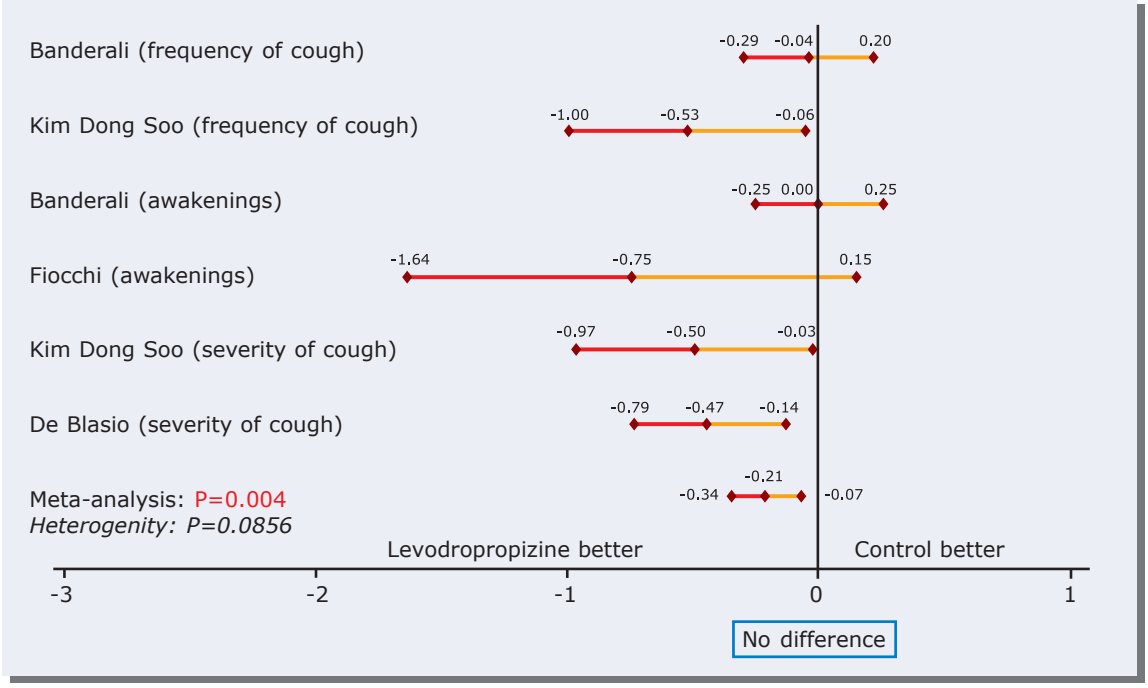
This standardized meta-analysis of published clinical studies, despite some limitations mainly linked to the small number of trials included in the analysis and the different efficacy variables assessed, provides an overview of the major comparative evidence on levodropropizine in terms of efficacy in the pediatric setting.

The results of our meta-analysis indicate that levodropropizine is an effective antitussive drug in children, showing stati-

Table 3. Meta-analysis of Overall Antitussive Efficacy (lLevodropropizine vs. Controls).

Levodropropizine vs. Controls	Standardized Mean Delta	95% C.I.		p
		Lower	Lower	
	-0.205	-0.344	-0.066	0.0044

Figure 1. Meta-analysis of the efficacy of levodropropizine vs. controls in pediatric studies.



stically significant better outcomes vs. central antitussive drugs (codeine, cloperastine, dextromethorphan) in terms of overall efficacy in reducing cough intensity, frequency and night awakenings.

These positive overall efficacy results are particularly important considering that levodropropizine is a very well tolerated peripheral antitussive drug[7], while centrally-acting cough suppressants may be associated with serious side effects that limit their use especially in children, thus further reinforcing the favorable benefit/risk profile of levodropropizine in the management of pediatric cough[1]. TiM

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