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Review Article

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Levocloperastine: A Review on pharmacodynamics, clinical efficacy, tolerability and safety in the treatment of chronic cough

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Cough is one of the most frequent respiratory signs reported in children and is one of the most common reasons for which parents seek medical attention for their child. Cough may be a distressing symptom, and empiric treatment with antitussive agents is often used. Current antitussive agents at effective doses have adverse events such as drowsiness, nausea and constipation that limit their use. There is a therapeutically need for more effective and better-tolerated agents. Levocloperastine is a centrally acting agent which is believed to inhibit cough primarily by their effect on the cough centre. The aim of this review was to evaluate the available evidence regarding efficacy, tolerability and safety of Levocloperastine for symptomatic treatment of cough. A total of 10 controlled clinical trials conducted both in adult and in children involving a total of 794 subjects have been carried out to evaluate efficacy safety and tolerability of Levocloperastine. Levocloperastine can produce a greater reduction in the intensity and frequency of cough compared with other antitussive compounds. Levocloperastine is an effective antitussive agent for the treatment of cough in patients of all age groups. It has a more rapid onset of action than standard agents with an improved tolerability profile. LCP represents a valuable alternative to currently used antitussive agents with the added advantage of faster onset of action and improved tolerability.

Key words: Levocloperastine, cough, review, acute respiratory diseases, anti-tussive agents.

INTRODUCTION

Cough is one of the most frequent respiratory signs reported in children and is one of the most common reasons for which parents seek medical attention for their child [1]. Cough could also profoundly and adversely affect the quality of patients' lives [2], especially if present at night n[3]. In most children, acute cough is due to viral upper respiratory tract infection (URTI), i.e., the common cold [4].

It is recognized that preschool and school children might suffer from acute respiratory infections 6 to 8 times a school year and can cough 140 coughs daily with a URTI [5]. Even if it is well known that cough should be considered a protective phenomenon and for this reason it is not mandatory "treat" this symptom, however cough resulting from URTI may be a distressing symptom, and empiric treatment with antitussive agents is often used [6]. Current antitussive agents at effective doses have adverse events such as drowsiness, nausea and constipation that limit their use [7]. There is also recent evidence that standard antitussive agents, such as codeine, may not so efficacious in reducing cough during upper respiratory infections [8]. Therefore, there is a therapeutically need for more effective and better-tolerated agents [9]. Among antitussive drugs available for the treatment of cough in children, codeine and cloperastine and Levocloperastine (LCP) are centrally acting agents (opioids and non-opioids) that are believed to inhibit cough primarily by their effect on the cough center [10].

The aim of this review was to evaluate the available evidence regarding efficacy, tolerability and safety of LCP for symptomatic treatment of cough. The efficacy and pharmacodynamics characteristics of LCP a novel antitussive, which acts both centrally on the cough center and on peripheral receptors in the tracheobronchial tree in treating chronic cough, was compares with that of

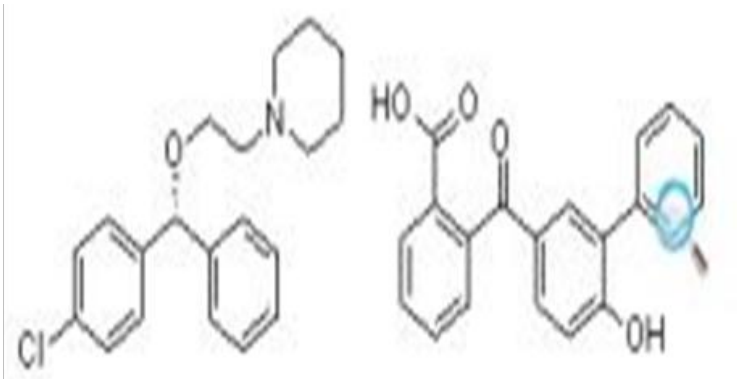

Figure 1. Chemical formula of Levocloperastine

other standard antitussive agents (codeine, levodropropizine and DL-cloperastine) in a total of 10 controlled clinical trials (analyzed by Aliprandi et al 2004) conducted both in adult and in children involving a total of 794 subjects.

Levocloperastine: Pharmacological Characteristics

a). Pharmacodynamics

LCP is the levorotatory isomer of DL-cloperastine [11] (Figure 1). LCP is an antitussive agent that acts both centrally, on the bulbar cough center, and peripherally, on the cough receptors in the tracheobronchial tree. This dual mechanism of action makes LCP very effective in the treatment of cough associated with many chronic and acute conditions in patients of all ages. In addition its action is highly selective improving the safety and tolerability profile of this molecule. More in details LCP is a non-opioid antitussive agent with a centrally active mechanism of action at the bulbar cough center. LCP has also an effect on peripheral receptors in the tracheobronchial tree.

Therefore LCP could be considered a dual antitussive agent. The antitussive effect on the bulbar cough center of LCP is highly selective therefore avoiding central adverse effects such as sedation. LCP is a non-narcotic antitussive agent with a chemical structure and a pharmacological profile distinct from cloperastine. In fact its chemical structure is distinct from that of racemate compound. This difference has also pharmacodynamics implications. The lack of adverse central effects seems in fact linked with the chemical configuration of the compound (levoisomer) in comparison with the racemic form. LCP does not interfere with mucociliar movements of respiratory tract mucosa.

The clinical use of LCP is not associated with sleepiness or agitation. Peristalsis is also not affected by LCP. These latter aspects are important characteristic regarding the safety and tolerability profile of the molecule. Finally LCP antitussive effect could be also ascribed to its antihistamine antiserotoninergic and muscle-relaxant actions and this could explain the clinical efficacy of LCP demonstrated in clinical trials.

b) Clinical Efficacy

Clinical efficacy of LCP has been evaluated and confirmed in several trials. At least 10 trials of whom 9 randomized and controlled, evaluating and comparing the efficacy of LCP with other antitussive agents are available (see Aliprandi et al [12]). In these studies a total of 740 patients have been enrolled. Of these two trials (involving 160 subjects) have been performed in pediatric (age 2-13 years) population. The antitussive efficacy of LCP has been compared with placebo (1 trial), codeine (2 trials), cloperastine (3 trials) and also levodropropizine (4 trials). The anti-cough effect of LCP was evaluated both in acute (i.e. viral upper tract infections) and chronic conditions. The studies enrolled patients of all ages with cough associated with various acute or chronic respiratory disorders including bronchitis, asthma, pneumonia and chronic obstructive pulmonary disease.

When compared with placebo or baseline conditions, LCP significantly improved cough symptoms (intensity and frequency of cough) in all trials, and improvements were observed after the first day of treatment. In children, LCP reduced nighttime awakenings and irritability, and in adults it was effective in treating cough induced by angiotensin-converting enzyme inhibitors. When compared with other antitussive agents, LCP had improved or comparable efficacy, with a more rapid onset of action. Importantly, no evidence of central adverse events was recorded with LCP, whereas drowsiness was reported by a significant number of patients receiving codeine. LCP is an effective antitussive agent for the treatment of cough in patients of all ages. It has a more rapid onset of action than standard agents with an improved tolerability profile.

In addition LCP is not associated with CNS detrimental effects such as drowsiness and reduction in attention levels. LCP is able in a dose response manner (30-120 mg/day) to reduce both cough intensity and cough frequency in

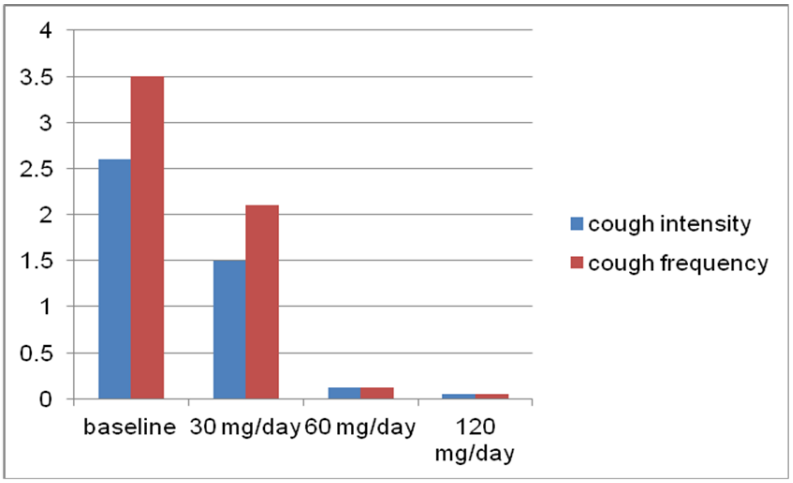

Figure 2. Antitussive effects of LCP and daily dosages.

comparison with baseline (Figure 2). All these trials showed that LCP improves cough symptoms. The efficacy of LCP was documented by a rapid decrease in cough frequency and intensity. This was also associated with a significant decrease in nighttime awakening due to cough.

Comparative clinical studies demonstrated LCP superior pharmacological effect over other antitussive agents currently used in cough medications. In 2004, a clinical trial was conducted in Italy by Aliprandi et al. [10], using children and adults as study participants. The majority of the children who participated had acute bronchial inflammatory conditions at the time, while adult subjects had chronic pulmonary disorders. The antitussive effects were observed as early as the first day of treatment, manifested by improved subjective, objective, and laboratory parameters. Objective measurements used in the study included reduction in cough frequency and intensity, nighttime disturbances, and difficulties in expectoration. Laboratory measurements included improvements on cardiovascular and respiratory parameters. The same study found out that LCP exhibited a faster onset of action with a substantial reduction in the intensity and frequency of cough. It was also generally well-tolerated by the body. Unlike codeine, it did not produce the adverse effects associated with the opiate agent such as sedation, sleepiness, dry mouth, nausea, and drug dependence. Moreover, LCP didn't interact with other drugs which make it a safe alternative for patients who take medications for other conditions. In the pediatric trials LCP efficacy was compared with levodropizine.

Both drugs improved clinical symptoms compared with baseline values. However there was a trend towards a more rapid improvement in patients taking LCP. In fact the percentage of patients showing improvement of cough symptoms at day 1 was 95% in the LCP group in comparison with 78% in the levodropizine treated group. In comparison with codeine LCP has shown, in two clinical trials involving 180 patients, to be at least as effective as the comparator.

C) Safety and Tolerability

An important aspect of LCP is that in comparison with other antitussive agents and particular opioids, this compound is characterized by favorable safety and tolerability profile. Clinical experience coming from the controlled trials shows that LCP in fact lacks clinically significant central adverse events. Clinical studies have shown that LCP in in general well tolerated. Mild and transient nausea was the only adverse event reported in clinical trials. There was no evidence of significant central adverse events, whereas drowsiness, dry mouth and nausea were reported with comparator agents (levodropropizine, codeine, DL-cloperastine). In animal studies no clinically relevant sedation effect has been observed with the use of LCP at doses up to 450-fold higher the therapeutic dose. LCP has no effects on the ability to drive and use of machine and this is a distinctive aspect in comparison with other antitussive drugs. No significant changes in laboratory parameters were observed. Overall in the comparative studies performed patients treated with LCP reported a low incidence of adverse events. For example drowsiness, quite commonly observed in codeine treated, was not reported in LCP treated patients.

DISCUSSION

Cough is a protective reflex serving a normal physiologic function of clearing excessive secretions and debris from the pulmonary tract. Cough in children is a common problem which should be managed by pediatricians [13]. Cough occurs more frequently in preschool than in older

children. Viral upper respiratory tract infections are the main causes of acute episodes of cough. The morbidity associated with acute cough in a child extends also to parents, teachers, and other family members. Cough causes concern for parents and is a major cause of outpatient visits. It can have a negative impact on quality of life, cause anxiety and affect sleep in parents and children. For this reason an immediate remedy is usually sought by parents. Therapeutic options for acute cough in children are limited due to the absence of drugs shown to be effective antitussives with an acceptable safety profile [14]. Anti-tussive products used for the management of cough in adults, such as narcotics (codeine), the non-narcotic opioid dextromethorphan, first-generation sedating antihistamines have all been considered inadequate for treatment of acute pediatric cough when a complete risk/benefit ratio is taken in account [15,16]. A growing body of evidence suggests that the peripherally acting antitussive, LCP, may be an attractive alternative for the treatment of bothersome acute cough in children. LCP is an antitussive compound with a pharmacological profile distinct from that of his racemic counterpart. LCP has a dual mechanism of action acting both on the central bulbar cough center and on peripheral receptors in the tracheobronchial tree. The antitussive effect on the bulbar cough center of LCP is highly selective therefore avoiding central adverse effects such as sedation. The lack of adverse central effects (sedation/excitement) seems to be link with its stereoisomeric properties.

Additional pharmacodynamic effects of LCP could be ascribed to its antihistamine, antiserotoninergic and muscle-relaxant actions. In preclinical studies, LCP demonstrated antitussive effects similar to those observed with opioids compound such as codeine. The available clinical trials conducted with LCP show that this compound has a faster onset of action and produces greater cough symptom intensity reduction compared with other widely used antitussive agents such as levodropropizine, codeine and DL-cloperastine.

Clinical improvements were observed as soon as the second day of treatment with LCP. From a safety and tolerability point of view LCP positively compares with other antitussive drugs. Preclinical studies have shown that in acute and repeated-dose toxicity studies, LCP was well tolerated, with no clinically significant cardiovascular or gastrointestinal adverse events. The pharmacokinetic behavior of LCP, best described by a two-compartmental model with absorption phase, is similar to that of the racemic compound DL-cloperastine. LCP is an antitussive agent that acts both centrally, on the bulbar cough center, and peripherally, on the cough receptors in the tracheobronchial tree. This dual mechanism of action makes LCP effective in the treatment of cough associated with many chronic and acute conditions in patients of all ages. In clinical trials, LCP has shown a rapid onset of action. In head-to-head trials LCP has demonstrated to produce a greater reduction in the intensity and frequency of cough compared with other antitussive compounds such as DL-cloperastine, codeine and levodropropizine. The pharmacodynamic action of LCP is also rapid: the antitussive effects (reduction in intensity and frequency of cough) of LCP were observed as soon as after the first day of treatment in patients of all ages. In children, LCP reduced night-time awakenings and irritability. LCP was generally well tolerated. There was no evidence of clinically significant central adverse events, whereas drowsiness, dry mouth and nausea were reported with comparator agents (levodropropizine, codeine, DL-cloperastine). So far LCP is the only central antitussive agent which, at therapeutic doses does not interfere with driving and use machines.

In addition LCP does not interfere with the mucociliar clearance.

CONCLUSION

LCP represents an effective alternative to currently used antitussive agents with the added advantage of faster onset of action and improved tolerability in all patient groups.

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