Efficacy and Tolerability of Levodropropizine and Clobutinol in Elderly Patients with Nonproductive Cough

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Summary

In a double-blind, randomised, clinical trial involving 191 elderly patients of either gender affected by nonproductive cough, the therapeutic efficacy and tolerability of oral levodropropizine and clobutinol (60mg three times daily for 3 days, for both agents) were evaluated. Efficacy was assessed by analysing cough intensity, the number of coughing spells in the 5 hours post-treatment, and night awakenings due to cough; tolerability was evaluated by analysing laboratory data, vital signs, dyspnoea and any adverse event occurring during the clinical trial, including the presence or absence of somnolence.

Independent of the underlying pathology, cough intensity was significantly (p < 0.01) reduced by both drugs at the end of the treatment period; moreover, the number of coughing spells was significantly (p < 0.01) reduced by both drugs after the first day of treatment. In addition to the relief of cough, the number of night awakenings was significantly decreased (p < 0.01) by both treatments. No changes in laboratory data were considered clinically relevant; vital signs were not clinically affected by either study drug. Mild somnolence was reported for a low percentage of patients (< 15%) with both drugs; the percentage of patients experiencing this adverse effect was about 50% lower with levodropropizine (6.5%) than with clobutinol (14.6%), although this difference was not statistically significant. Dyspnoea also improved throughout the treatment period.

These data indicate that both levodropropizine and clobutinol have antitussive efficacy and are free of bronchopulmonary adverse effects in elderly patients, although a central effect such as somnolence was experienced with a certain frequency, especially with clobutinol.

Physiologically, cough is a forced expiration to clear the airways of any agent or object causing obstruction, irritation or inflammation. Consequently, it can be viewed as a defence mechanism for the respiratory tract. Clinically, cough is often an indicator of an underlying respiratory illness where it does not perform a useful function, i.e. it does not clear the airways, either because there is
no real need for a defence tussive mechanism or because cough itself cannot accomplish its protective role. Indeed, cough is one of the most common reasons for seeking medical treatment, as recognised by a United States National Health Survey.\[1\]

An appropriate cough therapy is recommended in many conditions,\[2\] and should be specifically directed to more sensitive individuals such as children and the elderly. A wide variety of antitussive agents is now available, and they differ in their mechanisms of action. Opioid- (e.g. codeine, dihydrocodeine and dextromethorphan) and non-opioid-like (e.g. clobutinol) drugs are effective antitussives. These drugs act on the central nervous system, and thus also have different central adverse effects, such as somnolence, loss of alertness and vigilance,\[3\] and possibly also depressive effects on the respiratory system that may be relevant as a cough requiring therapy is often associated with pulmonary function is harmful, especially in old people.

Levodropropizine [S(−)-3-(4-phenyl-piperazin-1-yl)-propane-1,2-diol], the levo-isomer of dropropizine, is a non-opioid compound that has been proven to be an effective antitussive drug for cough associated with different lung pathologies, but without consistent central adverse effects.\[4,5\] Current data support a peripheral mechanism of action for this compound, possibly via a modulation of sensory C-fibre activation.\[4,6\] In addition, levodropropizine does not affect ventilatory parameters, the rheological properties of bronchial mucus, nor airway ciliary activity in patients with bronchitis.\[7\] In healthy subjects, after acute administration, it has no effect on specific airway conductance.\[7\]

We therefore planned a multicentre clinical trial in a population of elderly patients with nonproductive cough to confirm the efficacy of levodropropizine and its tolerability, in particular its absence of central adverse effects.

**Patients and Methods**

The efficacy and tolerability of levodropropizine administered to elderly patients presenting with nonproductive cough was evaluated in a double-blind, parallel-group randomised clinical trial conducted in 10 Italian centres. Levodropropizine was compared with clobutinol, which was chosen as a representative centrally acting non-opioid compound. Clobutinol is marketed in several European countries, including Italy, France and Germany, and its antitussive effectiveness has been demonstrated in several clinical studies.\[8,9\]

The study was performed in accordance with the Good Clinical Practice guidelines and was approved by the Ethics Committee of Istituto San Raffaele.

**Patients**

In- or outpatients aged more than 60 years, of either gender, attending the study centres for diseases characterised by nonproductive cough of at least moderate intensity were considered for inclusion in this study. Cough intensity was graded by the investigator on entry into the study according to the following scale: very severe (> 40 coughing spells/day); severe (31 to 40 coughing spells/day); moderate (15 to 30 coughing spells/day); mild (< 15 coughing spells/day); absent (0 to 1 coughing spells/day).

Patients with severe respiratory impairment, bronchial hypersecretion, neoplasia, tuberculosis, or progressive or unstable asthma were excluded. Patients receiving concomitant therapy with for example antitussive, mucoactive, antihistaminic or corticosteroid drugs were also excluded, as were patients with impaired cardiac, renal and hepatic functions.

All patients gave their informed consent to participate in the trial.

One hundred and ninety-one (104 males and 87 females) of 208 screened patients were recruited and completed the clinical trial. The mean age was 71.4 years (range 58 to 89 years); 2 patients in the levodropropizine group were enrolled at ages