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ScienceDirect
Phytomedicine 16 (2009) 17–24
Phytomedicine
www.elsevier.de/phymed

Tolerance, safety and efficacy of *Hedera helix*[1] extract in inflammatory bronchial diseases under clinical practice conditions: A prospective, open, multicentre postmarketing study in 9657 patients

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Abstract

In this postmarketing study 9657 patients (5181 children) with bronchitis (acute or chronic bronchial inflammatory disease) were treated with a syrup containing dried ivy leaf extract. After 7 days of therapy, 95% of the patients showed improvement or healing of their symptoms. The safety of the therapy was very good with an overall incidence of adverse events of 2.1% (mainly gastrointestinal disorders with 1.5%). In those patients who got concomitant medication as well, it could be shown that the additional application of antibiotics had no benefit respective to efficacy but did increase the relative risk for the occurrence of side effects by 26%. In conclusion, it is to say that the dried ivy leaf extract is effective and well tolerated in patients with bronchitis. In view of the large population considered, future analyses should approach specific issues concerning therapy by age group, concomitant therapy and baseline conditions.

Keywords: *Hedera helix*; Bronchitis; Safety; Efficacy

Introduction

Bronchial inflammatory diseases rank first among the causes for seeking primary care, and their symptomatic therapy with herbal extracts is broadly disseminated, particularly in European countries. Those products have been used for over 50 years, being the general perception that they are effective and safe. This is supported by the significant increase of their prescription in countries like Germany (Lemmer, 2001).

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doi:10.1016/j.phymed.2006.05.003

Haeberlein and coworkers have recently claimed that the secretolytic and bronchodilating properties found in *Hedera helix* extract are due to its content in saponins, particularly alfa hederin (Bedir et al., 2000; Trute et al., 1997) as an inhibitor of the β_2 receptors endocytosis, establishing an indirect β_2 sympathomimetic action (Hegener et al., 2004).

The drug's efficacy and safety have been documented in a series of clinical studies (Gulyas and Lämmlein, 1992; Laessig et al., 1996; Gulyas et al., 1997; Mansfeld et al., 1998; Hecker, 1999; Hecker et al., 2002) and although they differed in terms of objectives, methodology, populations and the respiratory diseases treated, they have provided evidence on the usefulness of this preparation in children and adults, which is not so frequent when speaking of a herbal-type preparation.

However, there are no large-scale studies available yet, carried out under usual clinical practice conditions, evaluating the usefulness of the preparation in the therapy of bronchial inflammatory diseases. A prospective, uncontrolled, multicentric trial was designed in Latin America to determine the efficacy and tolerance as well as the occurrence of adverse effects of *H. helix* extract in the suppression or relief of bronchitis-related symptoms, both assessed by the treating clinicians.

Materials and methods

Recruitment and enrollment of the target population

The subjects eligible for the study were patients of both genders, any age, living in Latin America, with a clinical diagnosis of bronchitis, and not meeting the exclusion criteria (see below). Bronchitis was defined as an acute or chronic bronchial inflammatory disease, associated with hypersecretion of mucus and productive cough, frequently associated with an infectious agent. Patients at initial stages, presenting with cough alone, were also included. The diagnosis was established by the treating physician in all cases and under the usual clinical working conditions.

The exclusion criteria were the presence of cardiovascular diseases, severe respiratory disease, kidney disease, history of hypersensitivity to *H. helix* extract, concomitant use of other mucolytic agents and/or cough relieving agents, known intolerance to fructose, pregnancy and breast-feeding.

After collecting the demographic and anamnestic data including the clinical characteristics of the relevant symptoms, (cough, expectoration, dyspnea and respiratory chest pain) the subjects enrolled were prescribed an appropriate therapy, which included the administration of *H. helix* to all patients, with or without other drugs, on the basis of the treating physician's initial clinical impression. Patients were then given an appointment within 7 days for a passive course control.

The patients were recruited at the outpatients' office and they (or their legal proxy) signed an informed consent to participate. Participants were requested to comply with therapy and follow-up visits. Patients were informed that they could drop out of treatment at any time, reporting the reason for the decision to the doctor.

Product under investigation

The product under investigation is a syrup containing dried ivy leaves extract (drug-to-extract ratio: 5–7.5:1; extraction solvent: ethanol 30% (w/w)). Dried extract of ivy leaves contains a mixture of several substances. Main constituents are triterpensaponins with hederacoside C as the predominant substance. At the moment it is not possible to trace the pharmacological activity of the extract back to one single ingredient. Therefore, the content of hederacoside C is determined to show a sufficient quality of the extract, because hederacoside C is discussed to be a part of the pharmacologically active principle. The minimum content of hederacoside C in the leaves is fixed at 30 mg/g dried leaves.

Administration of *H. helix* and control

The patients were instructed to take *H. helix* extract syrup (containing 700 mg ivy leaves dry extract (drug–extract ratio 5–7.5:1)/100 ml) for 7 days at the doses recommended by the manufacturer according to the patient's age:

- 0–5 years: 2.5 ml 3 × /day,
- 6–12 years: 5 ml 3 × /day,
- >12 years and adults: 5–7.5 ml 3 × /day.

Doctors were free to change the dosage or to discontinue therapy as required by the patient's response and the doctors' own clinical judgement. Patients were given the medication upon indication, baseline symptoms were documented and a passive control was performed: patients were instructed to attend a second visit, scheduled 7 days later; and doctors were then to record the parameters indicating tolerance, safety and efficacy. Whenever patients required a longer therapy with *H. helix*, the drug was provided free of charge.

Safety and efficacy assessment

The assessment tool was a perception survey to be answered by the treating physicians through a semi-closed questionnaire where the adverse effects, discontinuation of therapy, efficacy and tolerance were explicitly represented.