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Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. an other ivy leaves extract

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ABSTRACT

Ivy leaves extracts are authorised in medicinal products for the treatment of acute bronchitis. Different studies and the long experience on the market show safety and efficacy of this drug. A double-blind, randomised study was conducted to assess the efficacy and tolerability of ivy leaves soft extract with an other ivy leaves extract. 590 patients with acute bronchitis participated in this study. They were treated with test or comparator for 7 days (±1). The Bronchitis Severity Score (BSS) decreased gradually and to a similar extent from Day 1 to Day 7 in both treatment groups. Starting from values of 6.2–6.3 ± 1.2, the BSS decreased by approximately 4.7–4.9 points until Day 7, so that patients left the study with a mean BSS of 1.4–1.6. The BSS subscales cough, sputum, rhales/rhonchi, chest pain during coughing, and dyspnoea improved to a similar extent in both treatment groups. Overall, 2.7% of patients (per group and overall) experienced an adverse event, all of which were non-serious. Fewer patients younger than ten years had adverse events than would have been expected from their share of the study population ($p = 0.015$; Fisher's exact test). As a conclusion, the test product with ivy leaves soft extract proved to be non-inferior to the comparator ivy leaves extract in improving symptoms of acute bronchitis.

Introduction

Acute bronchitis is one of the main reasons for seeing a doctor and it is also one of the most frequent causes for days off work (Matthys 2004; Gonzales and Sande 2000). It is predominantly caused by viral infections, particularly the Respiratory Syncytial Virus (RSV), Coxsackie, influenza, parainfluenza, and ECHO-viruses or adenoviruses (Matthys et al. 2003). Treatment of uncomplicated acute bronchitis should be symptomatically orientated, but in practice it is frequently treated primarily with antibiotics. Antibiotics may be indicated in cases of bacterial superinfection, but generally they do not shorten the duration of uncomplicated disease. Therefore, medical associations like the Medicines Commission of the German Physicians (AKDAE) recommend treating patients with acute uncomplicated bronchitis primarily symptomatically (Recommendations of the AKDAE 2002).

In this symptomatic therapy so-called expectorants play an important role. A review of the Cochrane Collaboration, though in chronic bronchitis, showed that these drugs reduced exacerbations and days off work (Poole and Black 2001). One class of herbal expectorants, ivy leaves extracts, has had its long standing place in traditional medicine and its use was standardised by a Commission monograph of the German regulatory authority in 1988. The medication evaluated in this study conforms to this monograph.

Ivy leaves extracts have been well tolerated, with adverse effects generally limited to gastrointestinal reactions; very rarely also allergic skin reactions have been reported (Kraft 2004).

The mode of action of ivy leaves extracts has recently been elucidated. Originally it was assumed that the extract non-specifically stimulates the gastric mucosa and that parasympathicotonic reflexes in turn stimulate the secretion of bronchial mucus. Recent work, however, has shown that α-hederin, one of the active ingredients of the ivy leaves extracts, increases the beta-2-adrenergic bronchial reagibility. This leads to a relaxation of the smooth bronchial musculature and furthermore to an increased secretion of surfactant factors (Häberlein and Prenner 2005).

In several controlled clinical studies, the ivy leaves extract of the comparator product in this study has shown improvement of pulmonary function tests compared to placebo or active control. Furthermore a recently published open postmarketing study confirmed the safety and clinical effectiveness of the comparator in this study (Fazio et al. 2009). Non-interventional studies have examined the ivy leaves extract used in the test product in children up to 12 years of age. These studies showed safety and efficacy for this special patient group (Schmidt 2002a,b).

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Materials and methods

Plant extracts

The test product manufactured by Krewel Meuselbach GmbH (Hedelix drops, batch no.: 74842A) is authorised in several countries. The active substance, ivy leaves extract is produced from ivy leaves with an extraction solvent of 50% (v/v) ethanol and propylene glycol (98:2). The ethanol of this fluid extract was then removed by vacuum distillation. The volume of ethanol was supplemented by propylene glycol. The drug to extract ratio (DER) of the final spissum extract was 2.2–2.9:1. The dried ivy leaves comply with the Hederae folium monograph of the Ph. Eur. (2148). According to the Ph. Eur. the dried ivy leaves contain a minimum of 3% of hederacoside C, the main bidesmosidic triterpene saponine of the plant. Furthermore the plant and the extract contain small amounts of monodesmosides like α-hederin and flavonoids. The ivy leaves extract of the test product contains a minimum of 6.75% of hederacoside C.

The comparator product was obtained from a German wholesaler and manufactured by Engelhard Arzneimittel GmbH und Co. KG (Prospan drops, batch no.: 07B090B). The active ingredient is ivy leaves dry extract, extracted with 30% (m/m) ethanol and a resulting drug to extract ratio (DER) of 5–7.5:1.

The tested concentrations were in accordance with the recommended dosages of the authorised and commercially available medicinal products Hedelix drops and Prospan drops.

Study design, objectives, and outcomes

The study was performed according to ICH-GCP, the Declaration of Helsinki, the authorisation by the relevant national authority and the positive opinion of the involved Ethics Committee. The study was performed under the EudraCT No 2007-003272-19.

This study compared the efficacy and tolerability of two ivy leaves extracts in patients with acute bronchitis. The patients were recruited and randomised to one of two treatment groups: Hedelix® or Prospan®.

Patients took one of the medications three times daily over a period of seven days (±1). After the admission examination, patients returned for further examinations on Day 4 ± 1 and on Day 7 ± 1. Adverse events were documented between the time of informed consent and the last study visit.

The BSS (Bronchitis Severity Score) evaluates five symptoms, which are important for acute bronchitis: cough, sputum, rhales/rhonchi, chest pain during coughing, and dyspnoea. Each symptom was scored by the investigator on a scale from 0 to 4, with: 0: absent; 1: mild; 2: moderate; 3: severe; 4: very severe. The BSS is the sum of the five symptom subscores. Other clinical symptoms were scored on an identical 0–4 scale, global efficacy (investigators) and tolerability (investigators and patients) on five-step verbal rating scales. Body temperature was measured in °C, ability to go to work or school as a yes/no decision at every visit.

European regulatory guidelines on the performance of studies in acute bronchitis do not exist. So target criteria reflect clinical symptoms and are similar to those selected in other studies in acute bronchitis (Matthys et al. 2003). Due to the self-remitting character of acute episodes of bronchitis a parallel group design was chosen in preference over a cross-over study.

Patients

Male or female Caucasian patients at least 2 years of age with a confirmed clinical diagnosis of acute bronchitis and a BSS ≥ 5 were eligible for participation in the study. Patients had to present acute complaints, with duration of not more than 48 h.

Selection criteria excluded previous medications which may influence the course of the study indication or the evaluation of the target criteria, such as these stated under "Concomitant therapy". Furthermore, patients with concomitant diseases like allergic asthma or bronchial hyperreactivity, chronic bronchitis, other chronic or inherited lung diseases, or severe cardiac, hepatic, or renal disorders were excluded.

Children and adolescents were explicitly included in the study, because acute bronchitis is especially frequent in this population, which thus constitutes a major target population for the test product. Children under 2 years of age were excluded because of the excipient menthol in the test product.

Interventions, randomisation, blinding, and concealment of allocation

Hedelix® is authorised in several countries. The active substance, ivy leaves extract, is extracted with 50% ethanol with a resulting drug to extract ratio (DER) of 2.2–2.9:1.

Prospan® contains ivy leaves extract extracted with 30% ethanol with a resulting drug to extract ratio (DER) of 5–7.5:1. The calculated drug intake of the recommended daily dose is comparable in both medicinal products.

Patients were instructed to take the study medication three times daily in a dose of 24, 16, or 12 drops per dose, depending on age group (adults and children from an age of 10 years: 24 drops; children between 4 and 10 years old: 16 drops; children between 2 and 4 years old: 12 drops).

To permit blinding, the test product was fitted with a different drop former compared to the marketed product to have the same number of drops for both products.

Patients received the medication box with the next available number at the site. Treatment allocation was concealed and patients and study personnel at the sites, at the sponsor, and at the CROs responsible for study performance and statistical analyses were blinded to treatment assignment for the duration of the study until after the Blind Review Meeting.

Concomitant therapy

In general, concomitant medication for other indications was permitted during the study, but medication possibly influencing symptoms of acute bronchitis was excluded. These medications included beta-2 agonists, anti-viral drugs, antibiotics, corticosteroids, antihistamines, immunosuppressants, homeopathic drugs, household remedies or prophylactics for respiratory infections. Throat lozenges were permitted, but were not allowed within 4 h of a study visit. Paracetamol in a dose of up to 2 g per day was permitted, but was not allowed within 8 h of a study visit. Exceptions were allowed, if treatment for an acute condition became medically necessary. The investigators recorded all administered medications in the patient's case report form.

Sample size and statistics

Published studies in acute bronchitis using the BSS as primary endpoint found a standardised effect size Δ/s of active therapy vs. placebo of 0.64 and higher (Matthys 2004; Matthys et al. 2003; Chuchalin et al. 2005; Kemmerich et al. 2006).

The assumption was that also the test product and the comparator ivy leaves extract would show a similar efficacy. Following Röhmel et al. (2005) the border of non-inferiority for the comparison of the two drugs was set to approximately 50% of the expected effect of the active comparator vs. placebo, i.e. an effect size Δ/s of 0.32. To detect such a clinically relevant difference with a power of 95%, $n = 250$ evaluable patients per group were required (manufac-