Efficacy and safety of Herbion ivy syrup in patients with cough in acute bronchitis: comparison with a competitive brand with the same composition

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Key words
Acute bronchitis, productive cough, expectorant, ivy syrup, Hedera helix

Abstract

Aim of the study: *Evaluate the efficacy and safety profile of Herbion ivy syrup in comparison with a competitive brand with the same composition, Prospan syrup, in patients with cough in acute bronchitis.*

Subjects and methods: *A total of 126 patients were enrolled in the randomised, open, parallel, comparative and multicentre study. Sixty-three patients were randomised to receive Prospan syrup, and the other 63 to receive Herbion ivy syrup. Both products were taken orally for 7 days according to the prescribed dosing schedule each day of the therapy – 5 ml of syrup three times daily. The efficacy and safety assessments were carried out after 7 days of therapy. Additionally, safety and tolerability evaluation was done at day 4 of therapy and at day 14 (one week after the end of therapy).*

Results: *Improvement of cough was reported in 98.4% of patients in the Herbion and 96.8% of patients in the Prospan group. There was no significant difference between the two active treatments (Fischer's exact test; $p = 1.00$, lower 95% CI – 3.8 %). Complete relief of cough was reported in 16.1% of patients in the Herbion group and in 11.1% of patients in the Prospan group. Both treatments significantly ($p < 0.001$) reduced cough frequency and severity with comparison to baseline. The point estimates of mean change of frequency of cough for Herbion ivy syrup and the reference product were 2.03 and 1.86, respectively. The point estimates in cough severity for Herbion and the reference product were –43.6 mm and –42.9 mm, respectively. There was no significant difference between the two active treatments. Both products had very good tolerability. Adverse reactions occurred in 1.6% of patients in the reference product group and in 3.2% of patients in the Herbion group. The difference was not statistically significant.*

Conclusions: *Herbion ivy syrup was demonstrated to be an equally effective and safe therapeutic option as the reference product Prospan syrup for the treatment of cough in patients with acute bronchitis.*

Introduction

The *Hedera helix* (ivy) plant has been known for centuries for its healing-promoting effects in respiratory tract diseases.[1] The herbal medicinal product ivy leaf dry extract from the ivy plant is used in therapy as an expectorant in case of productive cough.[2] The ivy leaf dry extract has complex composition. It contains 2–6% of triterpene saponins, mainly hederacoside C and alpha-hederin, a small amount of other saponins (hederasaponins B, D, F, G, E, H and I), flavonoid glycosides, as well as the components of the essential oil.[3–5] Due to this composition the ivy leaf dry extract has multiple effects: expectorant effect, which is based on a secretolytic and mucolytic effect, and an anti-obstructive effect, which is caused by the bronchospasmolytic activity.[2, 5] The efficacy and very good tolerability of various forms of administration have been proved by the results of many clinical studies.[6–8]

The aim of our study[9] was to evaluate the efficacy and safety profile of Herbion ivy syrup in comparison with a competitive brand with the same composition, Prospan syrup, in subjects with cough in acute bronchitis.

Subjects and methods

Two formulations containing the ivy leaf dry extract were tested to establish comparative efficacy and safety profile between the two medicines. The patient population selected to test the efficacy of cough, with mucus or without mucus hypersecretion, involved subjects with acute tracheo-bronchial inflammation. A total of 126 patients were enrolled in the study. Of these, 63 were randomised to receive Prospan syrup (reference product (RP)), while the other 63 were randomised to receive Herbion ivy syrup (test product (TP)). The efficacy profile was not evaluated in one patient, while another patient had been receiving concomitant treatment that was not allowed in the study. In this article we used only the intention-to-treat analysis, which included 125 patients. The patients eligible for the study were: subjects with a cough-associated acute bronchitis (tracheobronchitis) with a score 3 or more on the scale of daytime cough frequency (0 – no cough, 1 – cough for a short period, 2 – rare cough during the day, 3 – frequent coughing that did not interfere with the usual daytime activities, 4 – frequent coughing that did interfere with the usual daytime activities, 5 – severe cough that made the usual daytime activities impossible); subjects of both sexes, 18–65 years, impaired ability to cough up sputum no more than 2 days prior to enrolment, the use of proper birth control method for women of child-bearing potential and signed informed consent.

The exclusion criteria were the presence of sinusitis, pregnancy and lactation, therapy with certain systemic medicines, hypersensitivity to the *H. helix* extract, severe respiratory diseases, pathological clinical states (malignant disease, cardiovascular, liver, kidney disease, etc.), clinically significant abnormalities in laboratory parameters and chest X-ray, alcohol consumption, drug abuse, patient's refusal to participate in the study or the patient had participated in another study in the last 15 days prior to the enrolment visit.

The study was randomised, open, parallel, comparative and multicentre. Patients were assigned to two treatment groups according to the randomisation schedule: one group received Prospan syrup (RP), while the second group received Herbion ivy syrup manufactured by Krka (TP). The investigated products had the same composition; both were syrups containing the ivy leaf dry extract (*Hedera helix L., folium*) (*5*–7.5 : 1), 7 mg. TP and RP were taken orally according to the prescribed dosing schedule each day of the therapy – 5 ml of syrup three times daily for 7 days at the doses recommended in the RP information documents. The efficacy and safety assessments were carried out after 7 days of therapy. Additionally, safety and tolerability evaluation (by a telephone interview) was done at day 4 of therapy and at day 14 (one week after the end of therapy).

The primary efficacy endpoint, the percentage of responders to the therapy, is one of the most relevant parameters for evaluating the efficacy of the therapeutic product in clinical practice and

was used in similar studies for the target indication.[6–8] The primary efficacy endpoint denotes the percentage of patients with improved or healed cough at the end-of-therapy assessment (% IHCO) and was assessed using a categorical cough-symptom rating scale (Table 1). Treatment success was defined as a grade 3 or 4 on this scale, assessed by the investigators. The % IHCO was calculated by the statistician based on the status of the subject at the end of therapy.

Category	Points
Complete disappearance of the symptom (within a week of therapy or upon completing week 1 of therapy – the patient's score is 0 at the end of therapy on the scale of daytime cough frequency)	4
Improvement of the symptom (the symptom persists but the frequency, volume and viscosity have improved causing the patient less disturbance within one week of therapy or upon its completion – the patient has a lower score on the scale of daytime cough frequency at the end of therapy than at baseline)	3
No change/no improvement of the symptom (symptoms remain unchanged since the first consultation and after completion of one week of therapy; the patient's general status has not changed either – the patient has the same score on the scale of daytime cough frequency at the end of therapy as at baseline)	2
Worsened symptom upon therapy completion (the symptom worsened during or upon completion of therapy – the patient has a higher score on the scale of daytime cough frequency at the end of therapy than at baseline)	1

Table 1. Cough relief/aggravation ratio scale

The following secondary endpoints were investigated: change in the frequency of cough (CFRC) and severity of cough (CSEVC) from baseline to the end of therapy and the percentage of patients with improved sputum colour (% ISPCL) and consistency (% ISPCN) at the end of therapy. A 6-point (0 to 5 points) categorical scale was used to assess cough frequency. For the severity of cough the Visual Analog Scale (VAS) was used. It is composed of a 100 mm line with the left hand labelled with the phrase "no symptoms" and the right hand labelled "maximum severity of a symptom". Sputum characteristics were evaluated by the investigator using a grading system after the inspection of the sputum. For sputum colour, the following four grades were used: transparent, white, yellow and green. However, for sputum consistency three grades were used: liquid, half-viscous and viscous. The % ISPCL and ISPCN were evaluated only in the patients with expectoration at the baseline.

To evaluate the safety profile an interview and physical inspection was used. Lastly the investigator assessed the overall rating on tolerability. Overall tolerability was scored as poor (adverse reactions which result in therapy discontinuation), moderate (moderate and transient adverse reactions, usually not resulting in a withdrawal of study medications), good (mild adverse reactions, no need for therapy discontinuation) or very good (no evidence of adverse reactions).

The principal aim of the study was to demonstrate that the test product is not inferior to the reference product in terms of treatment success (i.e. the proportion of successfully treated subjects) as well as demonstrate a comparable safety profile between the two products. To achieve the final goals of the study different statistical methods were used. Fisher's exact test was used for comparison of primary efficacy between the groups to assess the hypothesis that the test product was not inferior in comparison with the reference product. Non-inferiority was defined as the lower limit of the 95% confidence interval (CI) for the difference in treatment success rates between the two groups being greater (less negative) than –15%. For secondary efficacy endpoints CSEVC and CFRC t-tests were used, while for the % ISPCL and ISPCN chi-square tests were used. As for safety analysis, the comparison of incidence between the groups (the overall incidence of adverse reactions) was processed using the chi-square test. Lastly the investigator's overall tolerability rating was analysed with the Fischer's exact test.

Results

There were 128 patients screened for the study. There were 2 screening failures. One patient was prematurely excluded without efficacy evaluation due to an adverse event and consequent withdrawal of the patient's consent. Another patient was excluded due to receiving concomitant antibiotic therapy (disease aggravation). The results present the intention-to-treat statistical analysis and comprise 125 patients, 63 in the RP group and 62 in the TP group.

The mean age of the study population was 39.4 years; the population was composed of 59.5% women and 40.5% men. The mean body weight was 74.28 ± 11.82 kg and the mean body height was 170.75 ± 8.08 cm. There were no significant differences regarding the demographic data between the TP and the RP groups (Table 2).

		TP (n = 62)	RP (n = 63)	Total (n = 125)	p (diff. between the groups)
Age (years)		38.2 ± 12.2	39.4 ± 12.5	39.4 ± 12.8	0.609
Sex (%)	Male	46	34.9	40.5	0.276
	Female	54	65.1	59.5	
Body weight (kg)		75.38 ± 11.75	73.17 ± 11.87	74.28 ± 11.82	0.296
Body height (cm)		171.94 ± 8.08	169.57 ± 7.97	170.75 ± 8.08	0.101

Table 2. Demographic data for the TP and RP groups

The comparison of the baseline demographic data, health status, concomitant diseases and habits revealed no significant differences between the treatment groups, rendering them comparable in terms of efficacy evaluation. Likewise, the groups were homogeneous in terms of baseline characteristics of respiratory signs and symptoms which were also observed and analysed to assess the therapeutic effect of the medicines. There were no significant differences in baseline population characteristics.

Primary efficacy endpoint (% IHCO)

The primary efficacy endpoint analysis showed unequivocally that both therapies are highly effective in cough treatment. At the end of the therapy, a total of 98.39% of patients in the TP group and 96.83% of patients in the RP group reported improvement of cough (Figure 1). There was no significant difference between the two active treatments (Fischer's exact test; p = 1.00, lower 95% CI –3.8%).

A complete relief of cough was reported in 11.11% of patients in the RP group and in 16.13% of patients in the TP group.

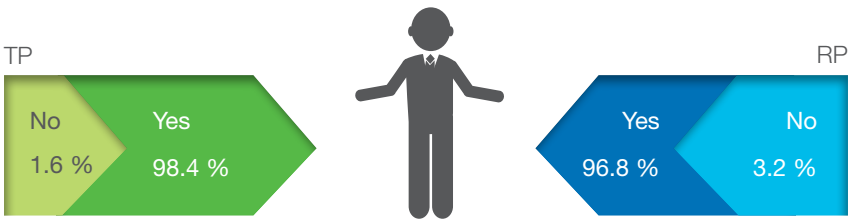

Figure 1. Percentage of patients with improved or healed cough – group comparison

Secondary efficacy endpoints

Change in the frequency of cough (CFRC)

The frequency of cough was reduced from frequent, disturbing daytime cough, to rare episodes of cough, which did not interfere with daily activities in both treatment groups. The endpoint denotes the mean change in the cough frequency score determined by the 6-point categorical scale at baseline and at the end of therapy. The point estimates of mean CFRC for Herbion ivy syrup and Prospan syrup were 2.03 ± 0.96 and 1.86 ± 0.86, respectively (Figure 2). The mean difference between the two investigational medicinal products was 0.175 points in favour of Herbion ivy syrup (p = 0.284, 95% CI: 0.147–0.497). There was no significant difference between the two active treatments.

Figure 2. Average decrease in the frequency of cough (points) – group comparison

The mean cough frequency score at the end of the treatment period in the RP and TP groups was 1.76 and 1.65 points, respectively. Both treatments significantly reduced cough frequency with comparison to baseline (p < 0.001).

Change in the severity of cough (CSEVC)

Cough severity was significantly reduced with comparison to the baseline as well. CSEVC was assessed with VAS. The mean cough severity at the end of therapy was 20.2 mm and 19.7 mm in the Prospan and Herbion groups, respectively. The point estimates at the end of therapy for Herbion ivy syrup and Prospan syrup were –43.62 mm and –42.90 mm, respectively (Figure 3). The difference between Herbion ivy syrup and Prospan syrup was 0.72 mm in favour of Herbion (p = 0.854; 95% CI: 8.51–7.06).

While there was no significant difference between the two active treatments, both of them significantly reduced cough severity in comparison to baseline values (p < 0.001).

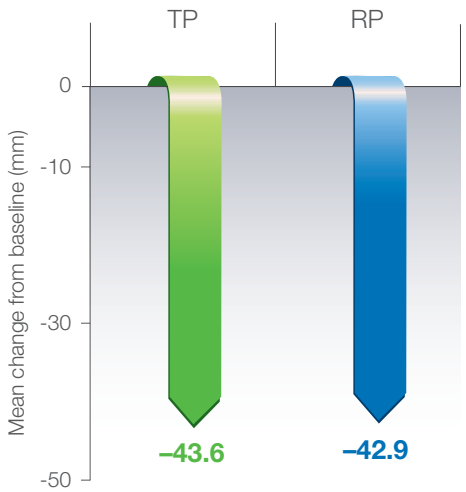

Figure 3. Change in the severity of cough – group comparison

Percentage of patients with improved sputum colour (% ISPCL) and sputum consistency (% ISPCN)

Sputum prevalence, which was more than 80% at baseline, was reduced to less than 50% in both groups. Both treatments substantially improved sputum colour and sputum consistency with respect to baseline. Both endpoints demonstrated no significant differences between the two treatments.
On average, 69.1% of patients reported improvement in sputum colour. In the Herbion group, 77.8% of patients achieved improvement in terms of sputum colour, while in the Prospan group the percentage of such patients was 60.7% (Figure 4). The difference between the two active treatments was non-significant in favour of Herbion (Pearson's chi-square test, p = 0.065). The distribution of 57 subjects with positive sputum occurrence at the end of therapy into sputum colour categories was almost identical in both groups (Pearson's chi-square test, p = 1.000).

Sputum consistency improved in 89.1% of patients. In the Herbion ivy syrup group, sputum consistency improved in 94.44% of patients. On the other hand, in the Prospan syrup group improvement was seen in 83.93% of patients (Figure 4). There was no significant difference between the two active treatments (Pearson's chi-square test; p = 0.124). The distribution of 57 subjects with positive sputum occurrence at visit 2 into sputum consistency categories was similar in both groups (Pearson's chi-square test; p = 0.245).

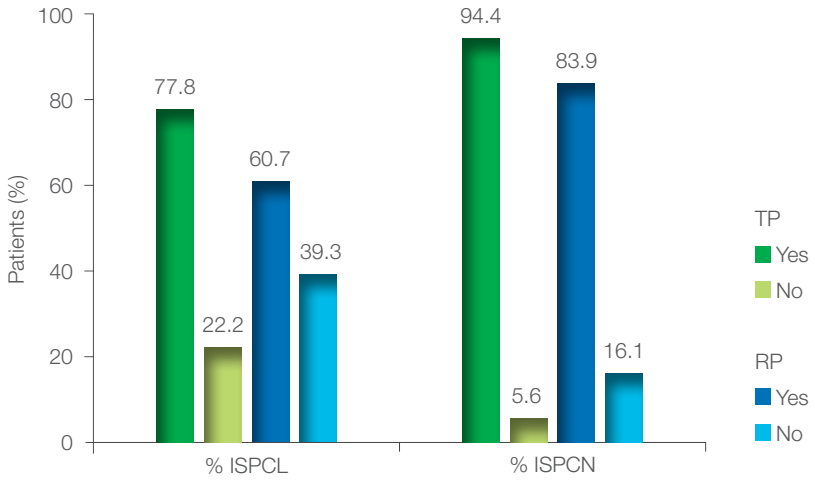

Figure 4. Percentage of patients with improved sputum colour and sputum consistency – group comparison

Safety

The number of adverse events was relatively low. Moreover, the overall tolerability rating demonstrated almost 100% excellent tolerability with no patients having low tolerability to the medicines. Statistically, no differences were detected.

The incidence of adverse events in the entire population was 2.4%. There were four adverse events documented in three patients. All adverse events were classified as adverse reactions (ARs). The overall AR incidence was 1.6% in the Prospan syrup group and 3.2% in the Herbion ivy syrup group. The difference was not statistically significant (Fischer's exact test; p = 1.00). Two patients experienced skin rash, one of them with concomitant itching, and one patient had nausea. Out of four ARs, two were mild and the other two were moderate. None of them was serious and all four of them were expected. One patient in the Herbion group prematurely concluded the treatment by his own decision due to a disturbing skin condition (the AR was not evaluated as clinically significant).

In the overall tolerability rating, assessed by investigators, 98.4% of patients were rated with a very good overall tolerability score (score 4), while in 1.6% of them (assigned to Herbion) tolerability was rated as good (score 3). The difference between the two groups was not statistically significant (Fischer's exact test; p = 0.496).

Discussion

In this study, Herbion ivy syrup as a tested medicine was compared to Prospan syrup, which is already marketed and was therefore an appropriate choice for the reference ivy leaf dry extract syrup. Herbion ivy syrup and Prospan syrup were tested in order to establish their therapeutic equivalence in the treatment of the target indication, i.e. acute tracheobronchitis. The study population was carefully selected to fit the condition according to the indication profile. The differences between the two treatment groups in baseline cough signs and symptom indicators were not significant. In addition, due to a very low drop-out rate, the results for comparison of safety of both syrups were rather homogeneous and therefore reliable.

The primary efficacy endpoint analysis unequivocally showed that the two therapies were highly effective in cough treatment. In comparison to Prospan syrup, Herbion ivy syrup therapy resulted in the equal level of treatment success, which was over 90% in both groups. In terms of secondary endpoints referring to cough frequency, severity and sputum characteristics, there were no clinically significant differences between the two therapies. In comparison with the baseline status both treatments significantly improved all the tested endpoints.

The safety profile analysis demonstrated a low frequency of adverse reactions with a very good overall tolerability rating. No significant differences in the safety profile emerged between Herbion ivy syrup and the reference product.

Conclusions

Herbion ivy syrup was demonstrated to be comparable and therapeutically equivalent to Prospan syrup in the treatment of cough in subjects with acute tracheobronchitis.

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