

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.

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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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Haerberlein 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 $\times$ /day,
- 6–12 years: 5 ml 3 $\times$ /day,
- > 12 years and adults: 5–7.5 ml 3 $\times$ /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.

The symptoms considered for efficacy were cough, expectoration, dyspnea and respiratory chest pain, before and after the treatment with the syrup under study.

Efficacy was evaluated as the overall change of symptoms in a scale considering: (a) the complete disappearance of cough, expectoration, dyspnea and respiratory chest pain within the week of therapy with *H. helix* or upon completing 1 week of therapy; (b) improvement of cough and/or expectoration, dyspnea, respiratory chest pain; these signs persist but their frequency, volume and fluency have improved, causing the patient less disturbance within 1 week of therapy or upon its completion and (c) no changes. The symptoms remain unchanged since the first consultation and after having completed 1 week's therapy; in general terms, the patient's general status has not changed either; (d) cough, expectoration, dyspnea and respiratory chest pain have worsened during or upon completion of one week's therapy. In general, the patient's status has worsened. Tolerance was determined by using the following scale: (a) very good–good: no evidence of adverse effects; if discontinuation of therapy occurs, it is by no means due to adverse effects; (b) moderate: adverse effects do occur but they are moderate or transient and they do not usually result in withdrawal of medication with *H. helix* and (c) poor: there are adverse effects and they result in discontinuation of therapy.

Signs and symptoms were considered to be adverse effects if they could not be reasonably attributed to the underlying condition, if they occurred during the period of therapy with *H. helix* and when they could be certainly or probably attributed to the intake of the drug under study. The presence or absence of adverse effects was recorded. In case of occurrence, free space was provided in the documentation sheet for details.

Discontinuation of therapy includes all the cases in which the administration of *H. helix* was discontinued by the patient, the treating physician or another doctor, whatever the reason.

As this research was a postmarketing study, with a product just being available at the market and where the documentation only included findings to be documented by the doctor during daily practice, an ethics approval was not necessary.

Statistical methods

The arithmetic mean and the median of the patients enrolled were considered as numeric variables in the description of the population. The category variables are expressed as percentual proportions with their appropriate 95% confidence interval (95% CI), calculated through Fleiss's square method.

Although the proportions of efficacy, tolerance and adverse effects are considered globally, given that in this study *H. helix* was administered to patients regardless of age, results are also considered and compared by age ranges: ≤ 15 years (children) and > 15 years (adults).

Results

Patients

A total of 10,562 patients were recruited by 3287 doctors participating in the study in 11 Latin American countries during a 23-month period (January 2003–November 2004). Both the patient inclusion data and the onset of symptoms were recorded. From the patients recruited and enrolled, 905 were not eligible for analysis because they did not show up for the follow-up visit. The population finally evaluated was 9657 patients (Table 1), consisting of 5181 children (53.7%) at the age of 0–14 years (median 5.5) and 4476 (46.3%) adults aged 15–98 years (median 41.9). An age range breakdown of participating children is shown in Table 2. All patients (100%) suffered from cough, 74.5% from expectoration, 22.0% presented dyspnea and respiratory-related chest

Table 1. Distribution of the 9657 Latin American patients with bronchitis included in the *Hedera helix* syrup therapy study

Countries	Evaluated patients
Argentina	1415 (14.7%)
Central America	76 (0.7%)
Chile	434 (4.5%)
Colombia	239 (2.5%)
Dominican Republic	150 (1.6%)
Ecuador	149 (1.5%)
Mexico	4894 (50.7%)
Paraguay	118 (1.2%)
Peru	950 (9.8%)
Uruguay	154 (1.6%)
Venezuela	1078 (11.2%)
Total	9657 (100.0%)

Table 2. Participating children according to age range

Age range	Children
<1 year	188 (3.6%)
1–5 years	2822 (54.5%)
6–12 years	1843 (35.6%)
13–14 years	328 (6.3%)
Total	5181 (100%)

Table 3. Characteristics of evaluated patients

	All	Children	Adults
Patients	9657	5181 (53.7%)	4476 (46.3%)
Duration of symptoms (median in days)	4	3	5
Duration of treatment (median in days)	7	7	7
Dose (median in ml/day)	15	10	22
Concomitant medication	5865 (60.7%)	3064 (59.1%)	2801 (62.9%)
Antibiotics	3795 (39.2%)	1874 (36.2%)	1921 (42.9%)

Table 4. Global rating of tolerance by the physicians

Tolerance	<i>n</i>	(%)	CI95%
Very good–good	9333	96.6%	(96.3–96.9)
Moderate	136	1.4%	(1.2–1.7)
Poor	78	0.8%	(0.6–1.0)
Not available	110	1.1%	(0.9–1.4)

pain was present in 21.9%. The mean duration of symptoms was 4 days.

The median duration of therapy with *H. helix* syrup was 7 days, and the median dosage prescribed was 15 ml/day (10 ml in children and 22 ml in adults). Concomitant drugs were prescribed to 60.7% (5,865) of the patients, and in 3,795 of them (39.2%) the drugs were antibiotics (Table 3).

Tolerance and adverse events

The tolerance of the product was considered as good or very good in 96.6%. Only in 0.8% the tolerance was rated as poor and there were no data available in 1.1% (Table 4).

Adverse events were reported in a total of 2.1% of the patients (CI 95%: 1.8–2.4%) (Table 5), while 112 of these events (1.2%) were reported in children. Most of these events were gastrointestinal (GI) disorders. All adverse events were of mild and transient nature. 46 patients (0.5%) discontinued therapy due to adverse events (Table 7), mainly due to gastrointestinal disorders (18 with diarrhoea).

The 112 adverse events in children mostly were gastrointestinal disorders. Table 6 shows the adverse events according to age range.

Preterminations

Therapy was discontinued in 4% of the patients (CI95%: 3.6–4.4%) Most of them (1.9%) ended therapy due to improvement or disappearance of symptoms. In

Table 5. Number and kind of adverse events

	<i>N</i>	(%)	CI 95%
<i>Adverse events</i>	198	2.1	(1.8–2.4)
Gastrointestinal disorders	149	1.5	(1.3–1.8)
Diarrhea	75	0.8	(0.6–0.9)
Abdominal and epigastric pain	38	0.4	(0.3–0.5)
Nausea and vomiting	26	0.3	(0.2–0.4)
Dry mouth and thirst	6	0.06	(0.02–0.1)
Anorexia	2	0.02	(0.004–0.08)
Eructation	1	0.01	(0.0005–0.07)
Stomatitis	1	0.01	(0.0005–0.07)
Skin allergy and other allergic manifestations	10	0.1	(0.05–0.2)
Anxiety, restlessness, tremor	5	0.05	(0.02–0.1)
Headache	6	0.06	(0.02–0.1)
Drowsiness	4	0.04	(0.01–0.1)
Palpitation	4	0.04	(0.01–0.1)
Sweating	2	0.02	(0.004–0.08)
Others	18	0.19	

only 0.9% discontinuation was due to therapeutic failure (Table 7).

Efficacy

Improvement or absence of symptoms after treatment with *H. helix* was observed in 95.1% of the patients (Table 8).

Depending on the symptom considered, there was improvement or disappearance of cough and expectoration in 93% of the concerned patients, dyspnea and chest pain was improved or healed in 91% of the patients. (Table 9).

Strata according to concomitant therapy and age range

The concept of usual clinical conditions applied in the study (except for exclusion criteria) implied that patients

Table 6. Number and kind of adverse events according to age range

Children – age range	<1	1–5	6–12	>12
<i>Adverse events</i>	3	59	35	15
Gastrointestinal disorders	3 (100%)	55 (93%)	28 (80%)	13 (87%)
Diarrhea		39	14	6
Abdominal and epigastric pain		3	6	2
Nausea and vomiting		13	5	2
Dry mouth and thirst			2	1
Eructation			1	2
Skin allergy and other allergic manifestations		2 (3%)	2 (5.8)	2 (13%)
Anxiety, palpitations		1 (2%)	2 (5.8%)	
Headache			1 (2.8%)	
Drowsiness		1 (2%)		
Dizziness			1 (2.8%)	
Sweating			1 (2.8%)	

Table 7. Discontinuation of therapy (number and reasons)

	<i>n</i>	(%)
Discontinuation of therapy	388	4.00
Improvement or healing	186	1.90
No improvement	76	0.80
Worsening of symptoms	39	0.09
Adverse events	46	0.50
Concomitant illness	26	0.30
Taste intolerance	7	0.07
Others	5	0.10
Not specified	3	0.03

Table 8. Efficacy of therapy with *Hedera helix* syrup in 9657 patients with bronchitis related to changes of clinical symptoms

Efficacy	<i>N</i>	%	CI95%
Improvement or healing	9183	95.1%	(94.6–95.5)
No change	318	3.3%	(2.9–3.7)
Worsening	62	0.6%	(0.5–0.8)
Not available	94	1.00%	(0.8–1.2)

might receive only *H. helix*, but most received the herbal product plus antibiotics or the herbal product plus another medication (usually antipyretics, NSAIDs and antiallergics) or the herbal product together with antibiotics and another medication. Given this situation, the results were stratified and compared according to those possible therapies. Comparisons were performed through the relative risk (RR) with a 95% CI.

It could be shown that the efficacy of therapy with *H. helix* alone is comparable to that of *H. helix* plus antibiotics or other medication as mentioned above. The RR for adverse events when using *H. helix* alone is

significantly lower compared to the group receiving *H. helix* plus antibiotics (RR: 1.26, CI 95%: 0.86–1.84). It may be more than twice when other non-antibiotic medication is added to *H. helix* (RR: 2.34, CI 95%: 1.66–3.28).

The indicators considered did not show major clinical differences among adults and children, although efficacy was marginally higher among adults (Table 10).

Discussion

Significance

The current research with *H. helix* is the first to be conducted in Latin America; beyond the geographical aspect, the population differs from the perspective of the patient's social, cultural and ethnical background. Furthermore, this is a corporate study, involving more than 3000 doctors in 11 different countries. The large population enrolled places it as the largest prospective trial available for the treatment of bronchial conditions with *H. helix* syrup. Another aspect is that the study was performed under clinical practice conditions where other medication frequently is used. It is important to note that the only previous prospective and multicentric studies recording the administration of concomitant medication are those by Laessig et al. (1996) and Hecker (2002). Moreover, our work involves a very broad population with regard to age range and types of bronchitis.

Framework

Several studies have been conducted to show the safety and efficacy of the therapy with *H. helix* extract in inflammatory bronchial diseases. The results of such

Table 9. Incidence and evolution of symptoms in 9657 patients with bronchitis treated with *Hedera helix* syrup

	Cough			Expectoration			Dyspnea			Pain		
	<i>n</i>	%	CI 95%	<i>n</i>	%	CI 95%	<i>n</i>	%	CI 95%	<i>n</i>	%	CI 95%
Incidence	9657	100		7191	74.5		2129	22.0		2112	21.9	
Improvement or healing	9021	93.4	(92.8–93.9)	6677	92.9	(92.2–93.4)	1941	91.2	(89.9–92.3)	1917	90.8	(89.4–91.9)
No change	343	3.6	(3.2–3.9)	270	3.8	(3.3–4.2)	83	3.9	(3.1–4.8)	68	3.2	(2.5–4.1)
Worsening	58	0.6	(0.5–0.8)	27	0.4	(0.2–0.5)	6	0.3	(0.1–0.6)	5	0.2	(0.09–0.6)
Not available	235	2.4	(2.1–2.8)	217	3.0	(2.6–3.4)	99	4.7	(3.8–5.6)	122	5.8	(4.8–6.9)

Table 10. Efficacy, tolerance, adverse events and discontinuation of therapy for children and adults

	Children		CI 95%	Adult		CI 95%	RR (CI 95%)
Patients	5181	4476					
Efficacy ^a	4934	95.2%	(94–96%)	4301	96.10%	(96–97%)	1.01 (1.00–1.02)
Tolerance ^b	4991	96.3%	(96–98%)	4342	97.00%	(95–99%)	0.99 (0.99–1.00)
Adverse events	112	2.2%	(1–3%)	86	1.90%	(1–3%)	0.89 (0.67–1.17)
Discontinuation	197	3.8%	(3–5%)	191	4.30%	(3–5%)	1.12 (0.92–1.36)

^aImprovement or healing.^bRatings as very good to good.

studies are summarized in Table 11. Although those studies are not absolutely comparable, they offer a framework that allows us to analyze the results obtained in the current research.

Previous studies with the same product have reported an efficacy and tolerance comparable to ours, classifying the results with regard to efficacy as cure/improvement and good/very good tolerance.

Efficacy

Improvement/healing of the symptoms assessed by doctors was achieved in 95.1% of the patients in our study. These results are comparable to those of studies like Hecker's (2002), involving a population that only had chronic bronchitis but a broad age range. The levels of efficacy seem to be marginally lower than the rate of efficacy found in some studies that only enrolled children (Gulyas and Lämmlein, 1992; Laessig et al., 1996). In our study, the population was analyzed separately by age range, despite the efficacy was globally very good, we found efficacy was marginally better in adults than in children.

An aspect to be considered is the presumable effect of antibiotics on efficacy. This effect may have to be considered jointly with adverse effects and tolerance and in view of its interest it will be discussed in a specific paragraph.

Tolerance and safety

The large number of patients included allows us to draw stronger conclusions, especially with regard to

tolerance and safety of *H. helix* syrup. In this regard, safety appears to be very favorable, since there is evidence of good/very good tolerance in 96.6% of all patients. These results are comparable of those from previous studies and therefore confirm the positive findings concerning the safety of the product.

Adverse events in general were rare, occurring in only 2.1% of the patients and leading to discontinuation of therapy in only 0.5% of the cases.

Albeit low, our adverse event rate is higher than the rate reported in retrospective (Kraft, 2004) and prospective (Hecker et al., 2002; Hofman et al., 2003) studies, even in patients who received *H. helix* alone. This fact could be due to the criteria of adverse event assignment, their definitions and the design of the studies.

Concomitant therapy

Postmarketing studies with designs similar to our own have been published: under clinical practice conditions, efficacy and tolerance assessed by doctors and recording a concomitant or long-term therapy (antibiotics/chemotherapy broncholytic/antiasthmatics, nasal decongestants). In 73% of 113 children with obstructive airway disease (Laessig et al., 1996) and in 52% of 1350 patients aged 1–98 years with chronic bronchitis (Hecker et al., 2002) concomitant therapy was administrated. Laessig et al. (1996) do not report “significant interactions” but they do report a “negative effect on tolerability” with broncholytic and antiasthmatic agents. In none of the cases efficacy was considered on the basis of concomitant medication, especially antibiotics/chemotherapy.

Table 11. Methods and comparative results of various studies performed with *Hedera helix* extract (ivy leaves dry extract [drug–extract ratio 5–7.5:1]) between 1992 and 2004

Author year country	Recruitment	Target population	Design	N	Age	Evaluation of pulmonary function	Dose	Percent concomitant medication	Assessed by doctor efficacy (cured–improved)	Assessed by doctor tolerance (very good–good)	Percent adverse effects	Percent of discount
Gulyas (1992) Germany	Unicenter prospective	Children 4–10 years COB ^a	Uncontrolled UCPC ^b PMS ^a	26	6.4 (mean)	Yes improved significantly	Syrup 2.5–5.0 ml × 4 × day (28 days)	0% Washout	65.40%	100%	0%	0%
Lässig (1996) Germany	Multicenter prospective	Children 6–15 years ROAD ^c	Uncontrolled UCPC ^b PMS ^a	113	9.0 (mean)	Yes improved significantly	Syrup 2.5 ml × 6 × day (20 days)	73%	85.7%	98.2%	0%	2.6%
Gulyas (1997) Germany	Unicenter prospective	Children 10–15 years COPD ^d	Controlled crossover randomised double blind	25	NA	Yes improved significantly	Syrup 5 ml × 3 × day (10 days)	0% Washout	NA	NA	0%	0%
Mansfeld (1998) Germany	Unicenter prospective	Children 4–12 years asthma	Controlled crossover randomised double blind	24	7.8 (mean)	Yes improved significantly	50 drops/day (3 days)	0% Washout	NA	100%	0%	14.3%
Hecker (1999) Germany	Multicenter prospective	0–79 years IODRT ^e	Uncontrolled UCPC ^b PMS ^a	248	NA	NO	By fabricant (7–8 days)	NA	86%	98%	0.40%	NA
Hecker (2002) Germany	Multicenter prospective	1–98 years chronic bronchitis	Uncontrolled UCPC ^b PMS ^a	1350	44 (median)	NO	By fabricant (28 days)	52%	91%	NA%	0.40%	5.7%
Corporative (2004) Latin America	Multicenter prospective	0–98 years acute and Bronchitis	Uncontrolled UCPC ^a PMS ^a	9657	Children 5.5 adults 41.9	NO	By fabricant (7 days)	60.7%	95.1%	96.6%	2.1%	4.0%

PMS^a. postmarketing surveillance.

NA: not assessed.

^aCOB. chronic obstructive bronchitis.^bUCPC. under clinical practice condition (in everyday practice condition).^cROAD. recurrent obstructive airway disease.^dCOPD. chronic obstructive pulmonary disease.^eIODRT. inflammatory obstructive disease respiratory tract.

In this study, concomitant medication was used in 60.7% of the patients enrolled. Antibiotics were used in 39.2% of the patients, which seems to be quite a high rate. This is due to the fact that in Latin America, a lot of physicians generally prescribe antibiotics in case of bronchitis.

The very good tolerance of therapy was affected only when other drugs, especially non-antibiotics, were added to *H. helix* syrup. This was due to adverse effects caused by the additionally applied products. Hence, the RR risk for the occurrence of adverse events when comparing *H. helix* monotherapy versus therapy with *H. helix* and additional antibiotics/chemotherapy is increased by 26% whereas efficacy marginally increased for only <3%. This analysis shows that the application of antibiotics in case of bronchitis has no additional benefit which is evidenced by the very known fact that nearly all cases of bronchitis are caused by viruses where antibiotics do not show any effect.

By combining *H. helix* with other non-antibiotic medication the RR for the occurrence of adverse events increases more than twice (with no improvement in efficacy).

This clinical study, performed under usual clinical practice conditions and encompassing a large population with an extense age range, allows us to particularly emphasize the very good tolerance going in line with scarce adverse events of the *H. helix* syrup. High percentage of efficacy is also remarkable achieving levels comparable to those found in other studies. Further controlled clinical trials are required to provide more detailed information in special patient groups.

In view of the large population considered, future analyses should approach specific issues concerning therapy by age group, concomitant therapy and baseline conditions.

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