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Short communication

Observational study on the tolerability and safety of film-coated tablets containing ivy extract (Prospan® Cough Tablets) in the treatment of colds accompanied by coughing

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ABSTRACT

The only saponin drug currently prescribed in any significant amount in monotherapy medicines is ivy. This post-marketing surveillance study (PMSS) aimed at investigating the tolerability and safety of film-coated tablets containing ivy leaves dry extract (extracting medium: ethanol 30%, DER 5–7.5:1 [Prospan® Cough Tablets]) under practice conditions. Adults and children aged 11–85 years of both genders were included. A total of 330 patients suffering from colds accompanied by coughing or from chronic, inflammatory bronchial diseases were scheduled to undergo treatment for a period of at least seven days. The tolerability of the tablets was rated by means of questionnaires.

The results of this PMSS reflect the good to very good tolerability of the tablets in the global assessment by both, the practitioner (98.5%) and by the patient (96.4%). This is one of the reasons for the high acceptance and compliance (rated as 'good' in 98.8% of all cases). The safety not only regarding the administration form but also regarding the active substance is thus underlined once again.

Introduction

Hedera helix Linné (L.) or ivy is an evergreen cirrus belonging to the family of Araliaceae. It is the only saponin-containing herbal drug which is considerably used in monotherapy due to expectorant and bronchospasmolytic effects. A number of controlled clinical studies have demonstrated its respective therapeutic effectiveness using a dry extract of ivy leaves for human use prepared from an aqueous-ethanolic extract (extracting medium: ethanol 30%, Drug-Extract Ratio (DER) 5–7.5:1) (Meyer-Wegener et al. 1993; Lässig et al. 1996; Hecker 1997; Mansfeld et al. 1997, 1998). Thus ivy belongs to a group of particularly well researched phytopharmaceuticals (Schulz and Hänsel 2004; Stauss-Grabo et al. 2008). Aqueous extraction of its juvenile leaves has been used since the 19th century in traditional medicine for the treatment of respiratory disorders. Today various formulations of medicinal products containing ivy leaves dry extract such as syrup, effervescent tablets, drops, tablets and suppositories are available.

Recently the efficacy of this extract has been reviewed (Guo et al. 2006; Hofmann et al. 2003; Landgrebe et al. 1999). Besides catarrh of the upper respiratory tract, the Commission E monograph "Ivy leaves", the ESCOP and the HMPC monograph consequently also name the symptomatic treatment of chronic-inflammatory bronchial diseases with the accompanying symptom of cough as therapeutic indications (Kommission E 1988; ESCOP 2003; HMPC 2009). Based on this well documented and verified clinical and pharmacological efficacy the 'Study Group History of the Development of Medicinal Botany' of the University of Würzburg, Germany, selected ivy as the 'medicinal plant of the year' 2010, a nomination provided annually in Germany (Czygan et al. 2010).

The tolerance of different ivy extract-containing preparations with exception of the film-coated tablets has likewise been tested many times in various studies (Hecker et al. 2002; Bolbot et al. 2004; Fazio et al. 2006).

For a long time it was assumed, that saponins generally would be absorbed by the gastrointestinal tract only to a very small extent, if at all, and thus no systemic effects were to be expected following oral administration. In the year 2004, α-hederin, a triterpenesaponin from therapeutically used ivy leaf dry extract, was identified as the central molecule responsible for the therapeutic effect (Hegener et al. 2004; Runkel et al. 2005). This was confirmed by recent *in vitro* studies showing that the mucolytic and expectorant action of ivy is based on indirect β_2-adrenergic effects and that this is due to the saponins α-hederin and Hederacoside C, the latter of which is metabolised to α-hederin in the organism (Sieben et al. 2009). Under stimulating conditions α-hederin inhibits the intracellular uptake of β_2-receptors and leads to an increased β_2-adrenergic response of the cell. The description of α-hederin as the

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primary effective ingredient at a molecular level offered for the first time a plausible *in vitro* explanatory model for the pulmonary effects of ivy leaf dry extract observed in numerous clinical trials and therapeutically used in humans.

Materials and methods

Study drug

The study was performed with film-coated tablets each containing 25 mg of ivy leaves dry extract (extracting medium: ethanol 30%, DER 5–7.5:1 [Prospan® Cough Tablets]). In order to specify the content of ivy leaves dry extract used for the preparation of the study drug, the saponin Hederacoside C is used as the primary reference substance following the requirements of the European Pharmacopoeia (content of Hederacoside C used for the HPLC-quantitative analysis calculated via HPLC against ivy leaf standardised tincture CRS).

Study design

This study aimed at investigating the safety of the tablets under practice conditions. Therefore this PMSS was a purely non-interventional and open clinical trial following the regulatory requirements considering the German recommendations for registered drugs and the relevant ICH Guidelines.

Adults and children of both genders suffering from colds accompanied by coughing or from chronic, inflammatory bronchial diseases were included. The intake of other preparations containing ivy leaves dry extract was not allowed. Subjects were, however, allowed to take other medicines.

The patients were scheduled to undergo treatment for a period of at least seven days, taking at least two film-coated tablets twice daily, and have a final medical examination seven days after starting the treatment at the earliest. The tolerability of the tablets was rated by means of questionnaires.

This study was accepted by the responsible ethics committee and the competent German authority prior to the beginning of the study. Study planning, performance and documentation followed the principles of good clinical practice.

Patients

A total of 330 male and female adults of all ages, adolescents and children 12 years or older suffering from an acute catarrh of the upper respiratory tract or a chronic inflammatory airway disease were planned to be included in the PMSS.

Prior to inclusion, all patients or children's legal representatives gave their informed consent. In case of ineffective therapy, not acceptable adverse drug reactions (ADRs), non-compliance or any other important reason, the practitioner could have stopped the treatment, but all ADRs would have been documented for evaluation.

Study performance

The study was performed by ten practitioners in Thuringia, Germany in 2008. Prior to inclusion demographic data, medical history, concomitant gastrointestinal or respiratory diseases including drug treatment and any allergic disposition or previous use of ivy were documented. After end of treatment period a final examination was conducted. Any premature withdrawal, ADRs, changes in the planned treatment or in the treated respiratory symptoms and their therapy was documented including reasoning for any unplanned change.

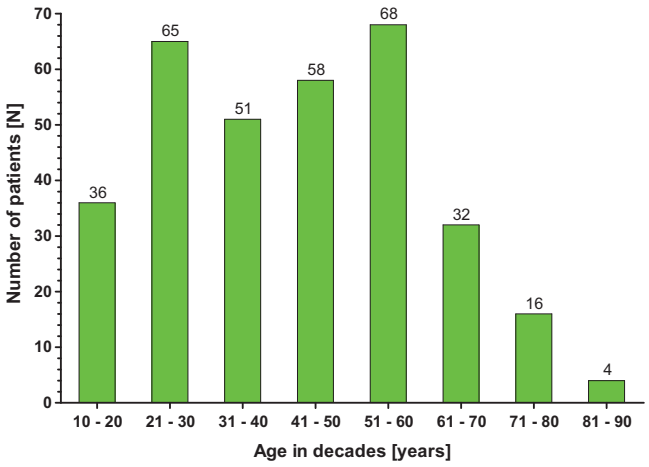

Fig. 1. Age distribution of all patients evaluable ($N = 330$).

As integral parts of the study objectives compliance was rated as 'good', 'moderate' or 'poor' and global assessment of tolerability was given by patient or patient's legal representative and practitioner using the following 4-point scale: 'very good', 'good', 'moderate' or 'poor'. Any ADR related to the treatment was documented regarding its intensity as 'mild', 'moderate' or 'severe' and causality as 'unlikely', 'possible', 'likely', 'certain', 'unclassified' or 'not evaluable' with documentation of time course and consequences.

Statistical evaluation

Data were subjected to descriptive statistical evaluation with graphical display, where appropriate. For demographic and dosing data means and medians including their percentages were calculated. For categorical data including compliance, global tolerability by patient and practitioner, ADRs, dosing data, treatment indication or concomitant diseases the absolute number per category and its percentages were given. ADRs were coded by MedDRA with the highest degree of intensity and causality for evaluation including time course and causality. All patients with at least one dose were included.

Results

Demographic and disease data

A total of 331 patients was included, 330 patients (206 female and 124 male) were evaluable. One female patient was excluded from the evaluation because she admitted not to have taken any dose of the study medication. Deviating from the study plan, an 11-year old girl was included and evaluated as well. Thus, patients included were between 11 and 85 years old (mean/median: 42/43 years). Fig. 1 shows that most of these patients were between 20 and 60 years old. The treatment was mainly initiated because of a catarrh of the upper respiratory tract with cough in 312 patients, accompanied by a chronic bronchitis in one case. Other indications were chronic bronchitis in twelve patients, COPD and pneumonia in one patient each as well as two and four other cases of acute bronchitis and not specified bronchitis, respectively. Concomitant gastrointestinal or other respiratory diseases were documented for 35 patients, most frequently bacterial bronchitis or COPD ($N = 9$ each), different types of asthma ($N = 6$) or chronic gastritis ($N = 5$). Twelve and four patients had a known allergy against drugs and environmental agents, respectively. None of the female patients were pregnant, but one woman was lactating.

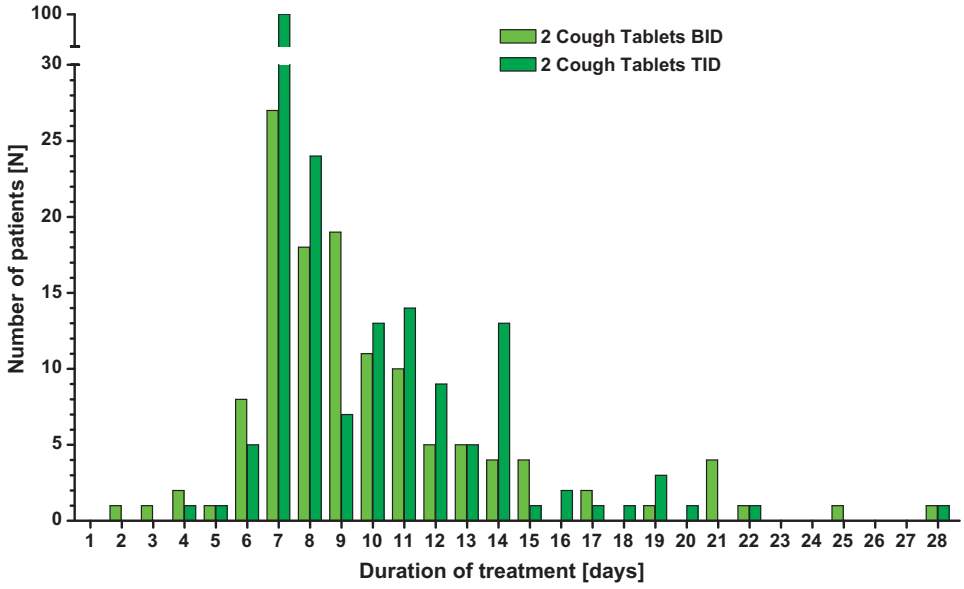

Fig. 2. Overall treatment duration ($N = 329$, the patient taking a dose of one tablet thrice per day not depicted).

Treatment data

A total of 310 patients received an at least 7-day treatment as planned, 113 patients with a twice daily dose of two tablets, 196 patients with a dose of two tablets thrice per day and one patient with a dose of one tablet thrice per day. The overall treatment duration was 2–28 days with 126 patients receiving two tablets twice per day, 203 patients with a dose of two tablets three times daily and the one patient with one tablet thrice a day. The median treatment duration was 8 days (Fig. 2).

Tolerability

During the treatment period no serious or unexpected ADR was reported. Within the evaluable group of 330 patients only one female patient reported an ADR that was possibly related to the treatment. She regularly experienced nausea of mild intensity without vomiting some 10 min after drug intake that lasted for approximately 30 min. This patient recovered without any intervention after end of treatment.

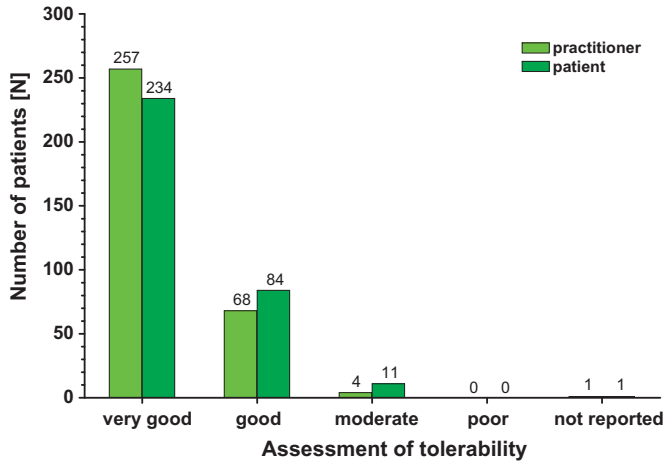

Fig. 3. Global tolerability judgment from 330 patients and their attending practitioner.

Fig. 3 illustrates the global tolerability by patients and their attending practitioners. A total of 318 (96.4%) of the 330 evaluable patients judged the treatment with Prospan® Cough Tablets as being 'very good' ($N = 234$ or 70.9%) or 'good' ($N = 84$ or 24.5%). Eleven patients (3.3%) rated the tolerability as 'moderate' without any preference for certain age groups. The practitioners documented a better tolerability for seven patients, who stated a ‚moderate' tolerability, while the remaining four patients (1.2%) had identical practitioners' assessment. Thus, for 325 (98.5%) of the 330 patients their practitioners stated a 'very good' ($N = 257$ or 77.9%) or 'good' tolerability ($N = 68$ or 20.6%). None of the patients or practitioners rated the tolerability as 'poor'. One patient experienced an acute gastroenteritis that was prevalent in the family and suspended the treatment. In this case, neither the patient nor the practitioner gave an assessment on global tolerability. Therefore a total number of 329 tolerability assessments resulted.

Only one case of 'moderate' tolerability could be related to the only ADR (nausea) that was rated as possibly treatment-related. No other peculiarity was apparent in any patient.

The practitioners rated the compliance as 'good' for 327 (99.1%) of 330 evaluable patients and as 'moderate' for three patients (0.9%). The assessment 'moderate' was given for one patient with a suspected non-compliance that was not confirmed by the patient and for another patient who refused the recommended third daily dosing. The third patient with an assessment of 'moderate' compliance was unwilling to follow the recommendation to stop smoking. Thus, compliance with the general therapy and only to a lesser extent with the study medication itself was the likely reason for this assessment by the practitioner.

Discussion

This observational study fulfilled the 'guideline on population exposure' (CPMP 1995) with a minimum requirement of 301 patients to detect (very) frequent ADRs with an incidence of at least 1%. In this study 330 patients were evaluated after a treatment with film-coated tablets containing ivy leaves dry extract (extracting medium: ethanol 30%, DER 5–7.5:1 [Prospan® Cough Tablets]). 310 of 330 evaluable patients received an at least 7-day treatment.

Both patients (96.4%) and attending practitioners (98.5%) documented a 'very good' to 'good' global tolerability of the treatment

which is considered to be the main reason for the extraordinarily high compliance. Moreover, only one 'possible' ADR occurred in this study: the reproducible occurrence of mild nausea shortly after dosing in one female patient that lasted for approximately 30 min.

This good to very good tolerability profile is in accordance with the results obtained from some other studies (Fazio et al. 2006; Hecker et al. 2002): for example in a study in 52,478 children of 0–12 years (Kraft 2004) the overall incidence of ADRs was 0.22% and predominantly of minor nature. The majority of 0.17% comprised gastro-intestinal symptoms. As a conclusion Prospan® Cough Tablets can be considered as safe and very well tolerable.

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