

TRANSLATION

Tolerability of dried ivy leaf extract in children

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Summary

Due to their secretolytic and bronchospasmolytic effects, preparations from ivy leaves are mainly used in the treatment of respiratory diseases in children. Results of a retrospective survey of 52,478 children (between 0 and 12 years) treated with alcohol-free cough syrup from dried ivy leaf extract, has confirmed the very good tolerability of the extract. The total occurrence of unwanted side effects was 0.22%. Gastrointestinal side effects with an incidence of 0.17% were the most important ones.

The prevalence of chronic obstructive respiratory disease, in particular chronic bronchitis (COPD), is increasing worldwide. In Germany, it is estimated that 10-30% of adults have a COPD, whereby 15-20% of those affected experience current symptoms due to respiratory obstruction. Quality of life is clearly reduced and the reduction of mean life expectancy without adequate therapy is about 10 years (5).



Ivy - fruit-bearing branch

The current therapy of choice is a staged treatment comprising inhalative, long-acting betamimetics and anticholinergics as well as the specific phosphodiesterase inhibitor theophylline. Antibiotics are only indicated for

exacerbations of bacterial origin and oral steroids are only required in case of severe exacerbations. Since COPD requires long-term therapy, good tolerability of the therapeutic measures used is very important. Current therapeutic recommendations by no means take phytotherapeutics into consideration to a sufficient extent. On the whole, expectorants are only recommended in patients suffering from a COPD with frequent exacerbations.

Dried ivy leaf extract: active substances, mechanisms of action

Over the longer term, dry extracts of ivy leaves could develop into a therapeutic option for evidence-based treatment of chronic obstructive respiratory diseases. A number of controlled clinical studies have now been published mainly for patients in childhood (4 years and older) confirming efficacy in cases of infections of the upper respiratory tract and obstructive pulmonary diseases. The extract has both secretolytic and broncholytic effects. The antitussive effect is particularly pronounced in cases of hypersecretion of viscous mucus (2). The main active substances are considered to be the triterpene saponins such as hederacoside C, at least 2.5% of which substances should be contained in the dried leaves. Then there are also small amounts of the hederasaponins B, D, F, G, E, H and I and the monodesmoside saponin α -hederin (10). In the most recent studies involving human lung epithelial cells (cell line A549), it was demonstrated that α -hederin inhibits internalization of β_2 -receptors and can thus enhance adrenergic response (3).

Studies performed

When considering long-term application in particular, as is required for chronic pulmonary disease, good drug tolerability is an essential factor. In the clinical studies published to date since 1990 involving preparations with and without alcohol in a total of approx. 300 patients, approx. 250 of them children, and exposures between 3 and 30 days (2), only one study reported two adverse drug effects (4%) with a causal connection to the therapy (6).

Two drug monitoring studies including a total of 1,396 children (0-16 years of age) with infections of the upper respiratory tract or chronic inflammatory respiratory tract diseases showed good to very good tolerability for both alcoholic and non-alcoholic preparations (syrup, drops) for application periods of up to two weeks (7). In a further drug monitoring study with children and adults suffering from chronic bronchitis (40.7% chronic obstructive bronchitis), an alcohol-free dry extract of ivy leaves (DEV 5-7.5:1; effervescent tablet) was administered over a period of four weeks. 1,349 patients, 165 of them children (4-12 years of age) and 128 youths (13-24 years of age), were included in the study. The recommended daily dose of 97.5 mg (4-11 years) and 130 mg of extract (12 years and older) was maintained by 82.4% of the patients. 5.7% of the patients discontinued the therapy - 0.3% due to adverse drug reactions (1 x nausea, 2 x eructation), 0.2% due to lack of acceptance, 1.6% due to non-compliance (1).

No systematic studies on the tolerability of dried ivy leaf extracts in infants and children up to 4 years of age had been published to date. This age group was explicitly included in the multicentric, retrospective data collection described below.

Patients and methods

The aim of the study was a data collection on the type and frequency of ADRs (adverse drug reactions) and the doctor's prescribed dosage of alcohol-free cough syrup with dried ivy leaf extract (DEV 5-7.5:1; Prospan® Cough Syrup). Data collection was done with structured questionnaires for the age groups < 1 year, 1-5 years, 6-9 years and ≥ 10 years; data collection was based on files kept by the physicians in charge of treatment for the months of January to June 2002 on patients with symptomatic respiratory tract diseases for whom the cough syrup had been prescribed. The duration of therapy was not recorded. Data evaluation was purely descriptive.

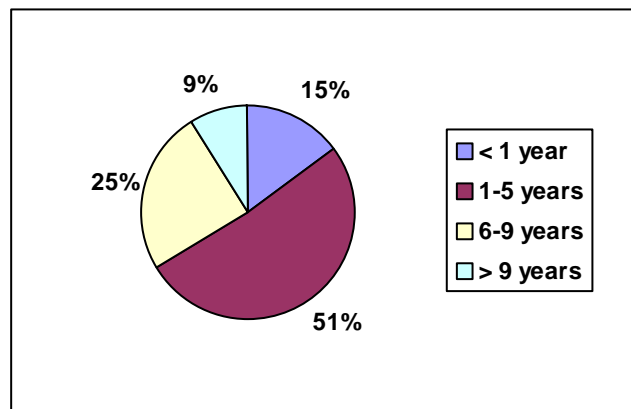


Fig. 1: Age distribution

Results

All told, the files of 52,478 children (0-12 years) with symptomatic respiratory diseases from 310 medical practices were evaluated. Most of the children (51%) were 1-5 years of age (Fig. 1). The daily dosage for children under 1 year of age as recommended by the manufacturer is 210 mg of drug (equivalent to 37.8 mg dried ivy leaf extracts). The mean prescribed amount was 227 mg. For children aged 1-5 the prescribed mean dose was 364 mg (manufacturer's recommendation: 315 mg of drug). For 6-9 year-olds and 10 years and older the manufacturer recommends 653 mg of drug / day (equivalent to 130 mg dried ivy leaf extracts). The prescribed amounts were 653 mg (6-9 years) and 710 mg of drug (10 years and older). Data on 52,077 children are available for this part of the evaluation.

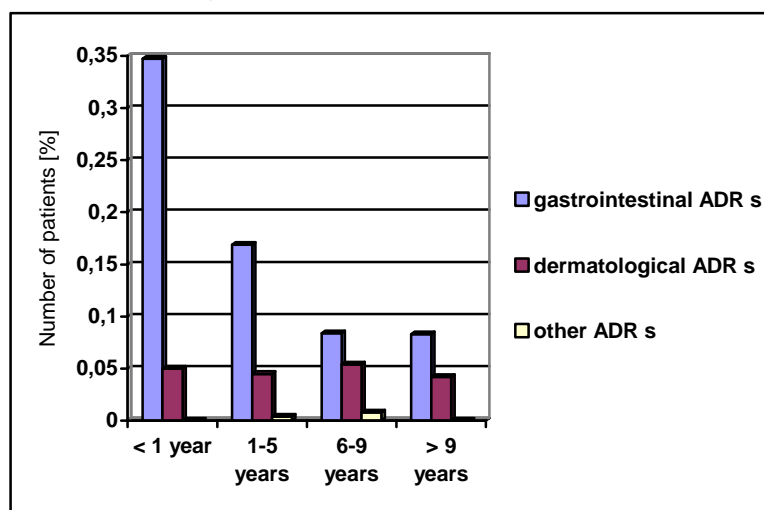


Fig. 2: Adverse drug reactions, according to age group in %

The total number of adverse drug reactions recorded in the patient files was 115 (incidence: 0.22%). The ADRs most frequently mentioned were diarrhoea (0.1%) and enteritis (0.04%), followed by allergic exanthema / urticaria (combined 0.04%) and vomiting (0.02%). Thus 0.17% of the children reported gastrointestinal complaints. The incidence of adverse drug reactions was age-dependent: It was 0.4% for children in their first year, whereby diarrhoeas accounted for the most cases at 0.27%, and 0.13% in children over 9 years of age (Fig. 2).

Conclusion

The present extensive retrospective study involving children confirms the known high level of tolerability of preparations made from ivy leaves, whereby the youngest age group was included here for the first time. Most of the gastrointestinal symptoms reported are presumably due to the sorbitol content of the cough syrup, since a laxative effect is known for sorbitol (11). The manufacturer's dosage recommendations were maintained in most cases, only in the oldest group was there a tendency to prescribe somewhat higher daily doses. Hence a very well tolerated phytotherapeutic secretolytic is available for obstructive pulmonary diseases in children, which has also demonstrated a bronchospasmolytic effect in vitro.

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Ivy (*Hedera helix*) - "*Klein Ephew*". Woodcut from: Leonhart Fuchs: *New Kräuterbuch* of 1543

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