

TRANSLATION

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**Clinical study: Treatment of children with chronic obstructive airways disease with Prospan®.**

## **Secretolysis and Bronchospasmolysis**

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Clinical study: Treatment of children with chronic obstructive airways disease with Prospan®.

## SECRETOLYSIS AND BRONCHOSPASMOLYSIS

The effects of the ingredients of dried ivy leaf extract (*Hederae heliis folium*) have been used therapeutically as an expectorant since ancient times. The purpose of prescribing expectorants is to prevent or eliminate mucostasis and ideally to reduce the relapse rate of infections.

### **Increase in mucociliary clearance**

The pathophysiological process of mucostasis is characterised by multifactorial causes. Effective elimination of mucus can be achieved by increasing mucociliary clearance, liquefying mucus and hence improving cough function with different drugs. The efficacy of dried ivy leaf extract has been acknowledged by the German supervisory authorities in the positive-list monograph and the licence for Prospan® drops in the indications of "coughs, colds affecting the respiratory tract and improvement of disorders in chronic inflammatory bronchial diseases," but not including the suppository dosage form.

Clinical studies in patients with chronic inflam-

matory bronchial diseases, such as bronchial asthma, are suitable for comparing the efficacy of different presentations, such as suppositories and drops. A validated method of demonstrating efficacy is offered by pulmonary function diagnosis using bodyplethysmography and spirometry, by which the secretolytic and bronchospasmolytic effect of dried ivy leaf extract can be demonstrated in respect of improvements in ventilatory disorders.

### **Study design**

In the case of therapy with suppositories for children, it should be borne in mind that they are generally accepted by children only over a short period of time.

Accordingly, the shortest possible period was

chosen in the clinical study to compare the efficacy of the suppository and drops dosage forms.

Clinical experience has shown that the secretolytic and bronchospasmolytic effect after treatment with dried ivy leaf extract occurs after a short time, so that a treatment period of 3 days may be considered clinically suitable. The efficacy and tolerability of dried ivy leaf extract children's suppositories and dried ivy leaf extract drops was to be compared in a randomised cross-over study in children with chronic obstructive airways disease.

### Patients/Methodology

The criteria of inclusion in the study comprised the signature of the declaration of consent by the parents or guardians, the diagnosis of "chronic obstructive airways disease" and an at least 10% reversibility of the bronchial obstruction. This was measured by determining the forced expiratory volume in 1 second without medication and 10 minutes after inhalation of 200 µg fenoterol and demonstrating an increase of at least 10%. Criteria of exclusion from the study comprised an airways resistance of > 0.9 (kPa/l/s), age < 4 and > 12 years and concomitant antibiotic therapy.

Dried ivy leaf extract suppositories for children and dried ivy leaf extract drops were administered as test substances. 100 ml of drops contained 2.00 g and 1 children's suppository contains 80 mg of standardised dried ivy leaf extract (5-7.5:1). In accordance with the manufacturers instructions, the children received 1 dried ivy leaf extract suppository twice daily for three days throughout the course of the study or 25

dried ivy leaf extract drops at 7.00 am and 7.00 pm according to the randomisation plan, following a wash-out phase of 2 to 4 days when administration of inhalational  $\beta_2$  -mimetics was permitted. The daily dose after administration of the children's suppositories and drops was 160 and 35 mg dried ivy leaf extract, respectively.

After collection of the data, all differential diagnoses of relevance to the study were noted and concurrent diseases documented. Over the whole 8- to 10-day treatment period, the children/parents or guardians were given a peak flow meter and asked to document the peak flow value daily at 7.00 am and 7.00 pm and to assess coughing, dyspnoea and expectoration. Any intolerance of the medication had to be documented in detail.

Airways resistance and the reversibility of bronchial obstruction was determined before the beginning of treatment.

Pulmonary function measurements were taken spirometrically on day 1 of treatment before administration and 3 hours after

medication by determining the forced expiratory volume in 1 second (FEV<sub>1</sub>), the forced vital capacity (FVC) and the peak flow value (PEF). On day 3 of treatment, in addition to spirometry, the target parameters of airways resistance, intrathoracic gas volume, residual volume and specific airways resistance were determined by bodyplethysmography.

It was ensured that no inhalational  $\beta_2$ -sympathomimetics had been administered 6 hours before the examination times for the pulmonary function diagnosis and this was noted in the documentation forms. It was established at all the pulmonary function measurement times that this was always done at the same time of day and that circadian variations in assessing changes in pulmonary function could be excluded.

**The improvements in pulmonary function proved to be clinically relevant and also statistically significant.**

**Table 1** *Forced expiratory volume in 1 second (FEV1)*

	Day 1 of treatment		Day 3 of treatment	
	Before medication	3 hours after medication	Before medication	3 hours after medication
Suppositories	1.35	1.52	1.37	1.64
Drops	1.38	1.59	1.39	1.61

**Results**

The clinical study was undertaken with 26 in-patients (11 girls and 15 boys) with a mean age of 7.2 years (range 5-11 years), a mean body weight of 25.6 kg (SD = 7.0 kg) and a mean height of 127 cm (SD = 11 cm). All patients were diagnosed as having bronchial asthma which had been present on average for 4.5 years (range 1-8 years).

No clinically relevant or statistically significant differences in the previous history associated with the allocation of the patients to the treatment sequence were detected.

**Significant reduction in airways resistance**

The initial airways resistance values in the reference measurements before the beginning of the study were less than 0.9 in all patients, with a mean of 0.64

(kPa/l/s). A mean airways resistance of 0.49 (kPa/l/s) was measured on day 3 after treatment with dried ivy leaf extract suppositories for children and of 0.44 after treatment with dried ivy leaf extract drops. The decrease in airways resistance from the initial value proved to be clinically relevant and statistically significant after both medications.

**Significant improvement in pulmonary function**

Measurements of forced expiratory volume in 1 second before the beginning of medication showed comparable initial values of 1.35 and 1.38 (l) (cf. Tab.1). The 12.6% mean increase on day 1 of therapy after treatment with the suppositories to 1.52 (l) proved to be comparable to the increase in the forced expiratory volume in 1 second to 1.59 (l),

corresponding to 15.2%, after treatment with the drops. The initial values on day 3 of treatment were almost the same in the two groups at 1.37 and 1.39 and resulted in a relevant and statistically significant increase to 1.64 and 1.61 (l), respectively.

The improvements in the forced expiratory volume in 1 second proved to be clinically relevant and statistically significant by a 2-tailed test procedure on both day 1 and day 3 of therapy after treatment with the suppositories for children and the drops.

The collation of the results of the mean measurements of forced vital capacity (FVC) shows clinically relevant and significant improvements of 0.27 (l) (from 1.54 to 1.81) after treatment with suppositories and 0.21 (l) (from 1.58 to 1.79) after treatment with drops (cf. Tab 2).

Table 2 Forced vital capacity(FVC)

	Day 1 of treatment		Day 3 of treatment	
	Before medication	3 hours after medication	Before medication	3 hours after medication
Suppositories	1.54	1.65	1.52	1.81
Drops	1.58	1.76	1.60	1.79

In terms of the peak flow values measured during the pulmonary function diagnosis, an increase from the initial value of 21.8% was found after the suppositories and 25.2% after the drops. The changes in peak flow values from the initial values were clearly correlated with the spirometric data obtained. In the comparison of the peak flow values entered on the patient record forms, a slight increase of 7 and 6 (l/min) respectively was obtained in the morning measurement after the two forms of treatment, whereas in the evening measurement at 7 pm there was no change. By contrast, during the washout phase a mean reduction of 4 (l/min) in the morning measurement and 12 in the evening measurement was obtained.

Questioning of the patients or parents/guardians

about the incidence and intensity of resting and exertional dyspnoea and about the cough analysis in respect of the intensity and frequency of coughing showed no clinically relevant changes or differences between the two treatment forms in the patient population studied.

**Very good tolerability**

The tolerability was rated by the doctor and the patients or parents/guardians as very good in 25 patients after both presentations. It was reported as moderate in only 1 patient after administration of the suppositories for children.

**Discussion**

The controlled clinical studies with dried ivy leaf extracts relate predominantly to treatments with alcoholic solutions from dried ivy leaf extract. The demonstration of

efficacy and safety for the biologically standardised dried ivy leaf extract (5-7.5:1) in an aqueous-ethanolic solution resulted in the positive-list monograph of dried ivy leaf extract and the licensing of Prospan® Drops by the German supervisory authorities.

**Therapeutically equivalent efficacy**

In the clinical picture of chronic obstructive airways disease, the secretolytic and bronchospasmolytic effect can be quantified by testing the changes in pulmonary function. The body plethysmographic changes in airways resistance on day 3 of treatment compared with the initial value showed a clinically relevant and statistically significant effect after treatment with the suppositories as well as with the drops. The verification of the chosen target parameters,

such as forced expiratory volume in 1 second, forced vital capacity, peak flow, intrathoracic gas volume, specific airways resistance and residual volume, confirmed comparable, clinically relevant improvements in pulmonary function after the two presentations.

The comparable efficacy of the two medications, based on the data measured by body plethysmography and spirometry, is underlined by the demonstration of therapeutic equivalence. This interpretation is validated by the fact that no cross-over effect or period effect was found. The combined results underline also that the treatment duration of only 3 days may be considered sufficient.

In conjunction with the pulmonary function tests, an increase in the peak flow value of 22 and 25% respectively was measured on day 3 of treatment, 3 hours after administration.

If this result is compared with the study findings from another study, according to which an increase of 32% in the peak flow value was determined in children 3

hours after oral ingestion of 2 mg salbutamol, the clinically relevant secretolytic and bronchospasmolytic effect of standardised dried ivy leaf extract becomes particularly marked. Although a comparison with the results of other studies must obviously be viewed cautiously, the data from this study indicate that the demonstrated effects in terms of the improvement in ventilatory disorder may be seen as a particularly pronounced pharmacodynamic effect of dried ivy leaf extract. This interpretation is supported by the pulmonary function diagnosis findings according to which the increase found in the determination of the reversibility of bronchial obstruction after inhalation of fenoterol to 1.61 (l) corresponds to the value on day 3 of treatment 3 hours after administration of dried ivy leaf extract of 1.61 and 1.64 (l) respectively.

The dosage of suppositories for children derived from pharmacokinetic results and taking into account the different absorption conditions has become established in practice and has been confirmed by the demonstration of therapeutic

equivalence with the dried ivy leaf extract drops at the manufacturer's recommended dosage. The demonstration of therapeutic comparability in respect of the improvement in ventilatory disorders shows that on rectal administration about 4.5 times the dose of the aqueous-ethanolic solution should be administered.

**With both presentations, marked secretolytic and bronchospasmolytic effects of dried ivy leaf extract and relevant improvements in lung function.**

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