

TRANSLATION

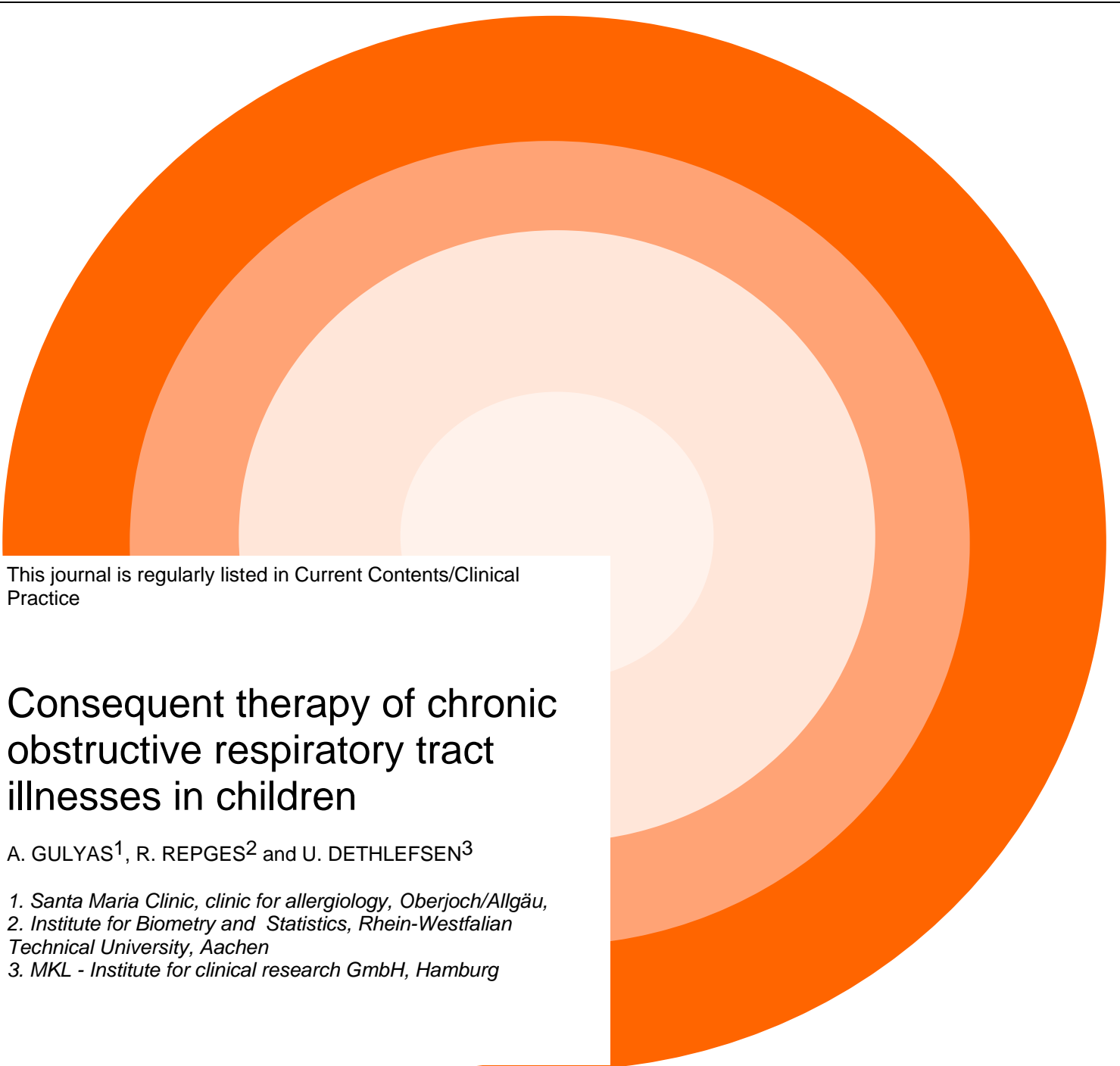
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Consequent therapy of chronic obstructive respiratory tract illnesses in children

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Therapy of chronic obstructive pulmonary diseases in children.

Dried ivy leaf extract has been appreciated for decades in the treatment of obstructive pulmonary diseases due to its bronchospasmolytic and secretolytic properties. In a randomised, double-blind, cross-over study changes in lung function were compared in 25 children at the age of 10 to 15 years suffering from chronic obstructive pulmonary diseases. The improvements of the bodyplethysmographic and spirometric parameters over a period of 10 days treatment were shown to be clinically relevant and statistically significant at the 10th day of treatment, 3 hours after application. Treatment with Prospan[®] Cough Syrup at a daily dose of 105 mg and Prospan[®] Herbal Drops with 42 mg of dried ivy leaf extract were shown to be therapeutically equivalent according to changes in lung function. The result of the study underlines the necessity of taking into account the different bioavailabilities of the active compound, when treating chronic obstructive respiratory tract illnesses with dried ivy leaf extract. Without the addition of ethanol, a remarkably higher dosage of dried ivy leaf extract is required to achieve an equivalent therapeutic effect in patients with chronic obstructive pulmonary diseases compared to solutions containing ethanol.

Key words: dried ivy leaf extract – chronic obstructive pulmonary diseases – lung function – therapeutic equivalence

Inflammatory bronchial diseases require early diagnosis and therapy over a wide level as a result of their common occurrence, their tendency towards dangerous progression and their symptoms, which initially often appear harmless [1, 6, 7]. Special action is particularly indicated for young patients, since it is possible that the patient may otherwise take a path towards a chronic pulmonary disease even at that age.

The prompt therapy regime, which if possible should follow early diagnosis, comprises the use of various tried and tested therapies.

Proceeding from the pathogenetic mechanisms of chronic obstructive pulmonary diseases, in addition to anti-inflammatory therapy, broncho-dilating therapy is also indicated and may be supported by secretolytic concomitant therapy. For the therapy of bronchial diseases which are accompanied by an inflammatory and hyper-reactive swelling of the bronchial mucous membrane, the elimination of the spasm in the non-striated bronchial muscles and mucostasis is extremely significant.

Clinical studies have shown that dried ivy leaf extract (*hederae heliis folium*) achieves a considerable improvement in the lung function of children suffering from chronic obstructive bronchitis [3, 4, 5]. According to these studies,

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improvements in impaired ventilation is not only due to the secretolytic effect of the contents of the dried ivy leaf extract, but also to its spasmolytic effect. This interpretation is underlined by the fact that Prospan[®] contains a dried ivy leaf extract, which has been standardised in terms of its spasmolytic effect.

The clinical picture of chronic obstructive pulmonary diseases offers a well-grounded clinical approach for proving the secretolytic and bronchospasmolytic effect of dried ivy leaf extract in validated conditions. The parameters used for the determination of the changes in lung function are ideal for evaluating this effect. Therefore, within the framework of a randomised, double-blind, cross-over clinical study, the effectiveness of Prospan[®] Cough Syrup without added alcohol and Prospan[®] Herbal Drops in an aqueous, alcohol solution, were compared with respect to the improvements they achieve in cases of impaired ventilation.

Methods

After receiving a positive vote from the Ethics Committee, the guardians of 27 in-patient children suffering from chronic obstructive pulmonary diseases gave their consent to take part in the study after receiving a detailed description of what was involved. The inclusion criteria comprised voluntary participation, an age of between 10 and 16 years, the diagnosis "chronic obstructive pulmonary disease" and an increase in the one-second capacity after inhalation of 200 µg of Salbutamol of in excess of 15%. The following were selected as exclusion criteria for participating in the study: a respiratory tract resistance in excess of 6 (mb/l/s), treatment with Theophyllin Retard preparations and a mucolytic agent or an anti-tussive three days before the start of the study and the use of a dosage aerosol with a β_2 -sympathomimetic, eight hours before the define dates for the study.

The preparations Prospan[®] Cough Syrup and Prospan[®] Herbal Drops, which are available from pharmacies, were selected as the test substances. According to the recommendations of the manufacturer, a dose of 5 ml of syrup three times per day is required for Prospan[®] Cough Syrup, which corresponds to 35 mg of dried ivy leaf extract per individual dose (daily dose: 105 mg of dried ivy leaf extract, which corresponds to 630 mg of active compound). For Prospan[®] Herbal Drops, a dose of 20 drops three times per day was selected, corresponding to 14 mg of dried ivy leaf extract per individual dose (daily dose 42 mg of dried ivy leaf extract, which corresponds to 252 mg of active compound). The medication was administered at 8 am, 2 pm and 8 pm over a period of ten days for each administration form. To ensure that the study was conducted in double-blind form, the double dummy technique was used, so that the patients were given both drops and syrup at all times, whereby one of the two administration forms was a placebo.

As a result of the blind nature of the study and its randomisation, it was not possible for either the doctor or the patients to tell whether it was the drops or the syrup which contained the actual medicaments.

The wash-out phase between medication I and medication II lasted for between two and four days.

It was ensured that the medication was administered at the same each day in all the studies to exclude the possibility of circadian fluctuations in the target parameters.

Lung function test

Before the start of the clinical study a measurement was conducted to find the reversibility of the bronchial obstruction by the determination of FEV₁ before medication and ten minutes after inhalation of 200 µg of Salbutamol. An increase of FEV₁ in excess of 15% showed that the patient met the inclusion criteria in terms of the reversibility of bronchial obstruction. The determination of the reversibility was conducted again, using the same method, after ten days of therapy with medication I and medication II to ensure that the initial and the final conditions of both sets of medication were comparable.

As part of the spirometric measurements the one-second capacity (FEV₁), the forced vital capacity (FVC), the vital capacity (VC) and the peak flow rate (PEF) one day before the application, on the fifth day after application and on the tenth day of therapy were measured before and three hours after the application of each medication with syrup and drops.

As part of the detail lung function diagnosis, before the start of the therapy on the first day and after the conclusion of the therapy on the tenth day, the respiratory tract resistance (RAW), the intrathoracic gas volume (ITGV) and the specific respiratory tract resistance (SRAW) were determined by bodyplethysmographic means.

The patient was allowed to take β₂-sympathomimetics by inhalation in emergencies; this had to be carefully documented in the patient records. It was also ensured by questioning that the patients had not taken any medicaments apart from the permitted constant accompanying medication for a period of at least six hours between the lung function diagnosis.

The main target criterion of the clinical study was to verify the comparability of the two medications in the sense of their therapeutic equivalence [2]. The changes in lung function from before the start of the

therapy up to the end of the therapy on the tenth day after medication were analysed as subsidiary target parameters by exploratory means, with a double-sided formulation of the question with non-parametric test processes for connected random samples as proposed by Wilcoxon.

Results

27 patients were included in the study in cross-over, randomised and double-blind fashion. In two patients the study was aborted as a result of intercurrent illnesses and the resulting additional therapy these necessitated which came under the exclusion criteria, which meant that the data of 25 patients can be regarded as complete.

The combination of the measurements on the lung functions under FEV₁ (l), FVC (l), VC (l) and PEF (l/s) is shown in Table 1 for all the measurement times from the first day of therapy before medication, the fifth day of therapy, three hours after medication, the tenth day of therapy before medication and 3 hours after medication during therapy with Prospan[®] Cough Syrup and Prospan[®] Herbal Drops. The measured mean values clearly show that after both Prospan[®] Cough Syrup and also after Prospan[®] Herbal Drops there is a clear clinical effect on the spirometric data which proved to be significant after therapy with Prospan[®] Cough Syrup and Prospan[®] Herbal Drops for the parameters FEV₁, FVC, VC and PEF and also from a statistical point of view.

The data obtained by bodyplethysmographic means for measuring RAW (ml/s), ITGV (l) and SRAW (ml/s) are shown in Table 2 in the form of mean values on the first day of therapy before medication and on the tenth day of

therapy, three hours after medication with Prospan[®]
as Cough Syrup and Herbal Drops.

Table 1. Spirometric mean values of lung function parameters one-second capacity FEV₁ (l), forced vital capacity FVC (l), vital capacity VC (l) and peak flow rate PEF (l/s) at the measurement times on the first day of therapy before medication, the fifth day of therapy three hours after medication and on the tenth day of therapy before and three hours after medication with Prospan® Cough Syrup and Prospan® Herbal Drops as per the "Per protocol data analysis" where n = 25.

	Syrup				Drops			
	1st day of therapy	5th day of therapy	10th day of therapy		1st day of therapy	5th day of therapy	10th day of therapy	
	before medication	3 hours after medication	before medication	3 hours after medication	before medication	3 hours after medication	before medication	3 hours after medication
FEV ₁	2.01	2.08	2.14	2.15	2.00	2.09	2.14	2.15
FVC	2.26	2.34	2.40	2.40	2.27	2.34	2.39	2.40
VC	2.37	2.44	2.49	2.49	2.37	2.45	2.50	2.50
PEF	4.44	4.64	4.83	4.91	4.44	4.75	4.87	4.91

Table 2. Bodyplethysmography. Mean values of the lung function parameters respiratory tract resistance RAW (mb/l/s), intrathoracic gas volume ITGV (l) and specific respiratory tract resistance SRAW (mb·s) at the measurement times on the first day of therapy before medication and on the 10th day of therapy three hours after medication as per the "Per protocol data analysis" where n = 25.

	Syrup		Drops	
	1st day of therapy before medication	10th day of therapy 3 hours after medication	1st day of therapy before medication	10th day of therapy 3 hours after medication
RAW	3.77	3.39	3.74	3.39
ITGV	2.78	2.59	2.76	2.59
SRAW	9.93	8.30	9.81	8.29

Table 3. Reversibility. Mean values of the determinations of the reversibility of the bronchial obstruction after inhalation of 200 µg of Salbutamol before and after ten days of medication with dried ivy leaf extract as per the "Per protocol data analysis" where n = 25.

	Before medication		After 10 days of medication	
	Control FEV ₁	10 minutes after inhalation of 200 µg of Salbutamol FEV ₁	Control FEV ₁	10 minutes after inhalation of 200 µg of Salbutamol FEV ₁
Syrup	2.00	2.46	2.15	2.45
Drops	2.00	2.44	2.15	2.45

The improvement in the objective bodyplethysmographic target parameters shows a clinically relevant and statistically

significant improvement in the lung function after both forms of therapy. A comparison of the improvement after Prospan® Cough Syrup

by 0.38 and after Prospan[®] Herbal Drops by 0.35 (mb/l/s) for respiratory tract resistance, by 0.19 and 0.17 (l) respectively for the intrathoracic gas volume and by 1.63 and 1.52 (mb•s) respectively for the specific respiratory tract resistance, shows that the pharmacodynamic parameters in both collectives underwent a considerable improvement in the same way.

To determine the therapeutic equivalence, the area beneath the curves for the measured RAW respiratory tract resistance values were evaluated. The areas measured using the trapezoidal rule beneath the curve for the objective lung function diagnostic parameter respiratory tract resistance, produced comparable values. A statistical test verified that both forms of therapy can be regarded as therapeutically equivalent.

The results of the clinical study also show that no side-effect occurred during the therapy with both administration forms of Prospan, whilst the preparation produced good effects and tolerance.

Discussion

The clinical evidence for the effectiveness of dried ivy leaf extract predominantly concerns treatment with alcoholic solutions, whilst no controlled clinical studies in double-blind conditions after treatment with Prospan[®] Cough Syrup exist. The result of the controlled clinical study clearly showed that the improvements in impaired ventilation in patients with chronic obstructive pulmonary diseases can be verified in cross-over conditions after therapy with both administration forms. An effect which is very clear from a clinical point of view and is also significant

from a statistical point of view was found after therapy with Prospan[®] Herbal Drops and Prospan[®] Cough Syrup in terms of the change in the respiratory tract resistance measured by bodyplethysmographic means. The drop in respiratory tract resistance by 9.4% after treatment with Prospan[®] Herbal Drops proved to be equivalent to the drop of 10.0% achieved after therapy with Prospan[®] Cough Syrup, which in both cases can be interpreted as clinically clear.

The evaluations of the changes in the other lung function diagnostic target parameters such as vital capacity, forced vital capacity, intrathoracic gas volume, specific respiratory tract resistance and peak flow values underline the clinically clear and statistically significant improvement in lung function during therapy with both administration forms. As a result of all the measurements on the lung function diagnosis it was possible to show clear clinical effects.

The validity of the results was underlined by the determination of the extent of the reversibility of the bronchial obstruction before and after the end of each treatment (see Table 3).

The verification of the therapeutic equivalence and good tolerance means that the administration forms of Prospan[®] Cough Syrup and Prospan[®] Herbal Drops can be regarded as effective as far as current scientific knowledge shows.

It is important to remember in practice that administration forms without added alcohol require around a 2.5 times higher dose of dried ivy leaf extract to achieve the same pharmacodynamic effect as after therapy with

an aqueous ethanol solution of dried ivy leaf extract - such as Prospan® Herbal Drops.

According to the results of this controlled clinical study, the bioavailability of dried ivy leaf extract is increased by the addition of alcohol so that administration forms which do not contain ethanol require a considerably higher dose of dried ivy leaf extract to achieve the same therapeutic effects.

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