

T W S P E K T R U M

Effective and well tolerated

IVY LEAF EXTRACT IN CHILDHOOD AIRWAYS DISEASES

Experts reject sweeping condemnation of expectorants in the new drug prescription report. In view of the increasing problems in the health system and the need for cost savings, economic considerations are gaining increasing importance in medicine.

However, occasionally this results in totally overshooting the target and short-sighted cost reduction measures can easily lead to additional financial burdens, agreed the experts at a press conference in Frankfurt. For example, the hypotheses put forward in the new 1996 drug prescription report about so-called "disputed drugs," at least in relation to expectorants, in many respects directly contradict clinical findings and scientific knowledge, declared *Prof. D. Hofmann* of the Frankfurt University Paediatric Hospital.

THERAPEUTIC NIHILISM MUST BE AVOIDED

This contradiction applied particularly to the classification of expectorants as "disputed drugs" for which "no clinically relevant therapeutic effect has been demonstrated," Hofmann said, because the clinical efficacy in patients with acute or chronic productive cough of a series of substances broadly classed as being of dubious efficacy and unnecessary had been demonstrated many times in controlled clinical studies on the basis of the improvement in ventilatory disorders. Abandoning these medications would undoubtedly have a detrimental effect on patients, particularly in paediatrics, according to Hofmann. Specifically in the numerous seasonally-related childhood respiratory tract infections, the recommendations of the drug prescription report and the KBV (Federal Association of Panel Doctors) were equivalent to therapeutic nihilism which in his opinion was unacceptable.

The drug group of expectorants includes substances which either have a purely secretolytic effect (secretolytics/mucolytics) or, in addition to broncholysis, also cause stimulation of ciliary movements by means of which the mucus is transported from the peripheral to the central bronchi and can then be coughed up (bronchospasmolytics). Mucolytics of clinical relevance include ambroxol and N-acetylcysteine, for each of which there are positive-list monographs. The secretomotor bronchospasmolytics include dried ivy leaf extract (Prospan®) and β -sympathomimetics, whose action has also been clearly confirmed in clinical studies.

TO SUM UP

Dr. H. Höhre: On the basis of its secretolytic and bronchospasmolytic effect, Prospan causes a marked improvement in ventilatory disorders and at the same time is very well tolerated.”

EXPECTORANTS NOT EQUIVALENT TO ANTITUSSIVES

Expectorants differ in their principle of action from antitussives, such as codeine preparations, which suppress the cough reflex by a dampening effect on the cough centre. As a result of ignorance of these pathophysiological relationships, expectorants and antitussives are frequently assessed jointly, sometimes even in the drug prescription report. Expectorants, however, do not suppress the expectoration of mucus, but eliminate or prevent mucostasis, liquefy the secretion and thereby facilitate coughing, Hofmann explained. The suppression of the cough stimulus during the day Hofmann even considers to be not without danger: the risk of pneumonia could be markedly increased as a result and antitussives should therefore never be used as alternatives for expectorants, he stressed. They are justified, however, when it is a matter of providing the patient and their family with an undisturbed night's rest.

HIGH VALUE IN PAEDIATRICS AND GERIATRICS

The importance of drugs for bronchitis and chronic respiratory tract diseases in clinical practice is apparent simply from the prescription figures: in 1995 more than 82 million prescriptions for expectorants and antitussives were given, and together these 2 drug groups were second among all the indication groups. Almost 92% of the prescribed daily doses involved expectorants. Mucolytic drugs were used particularly frequently in children up to 10 years of age and in elderly patients.

These recorded prescription figures do no more than reflect known morbidity data and medical necessities. All paediatricians know that small children suffer a bronchial condition 2 – 3 times annually. Likewise, all practising doctor knows that small children and, in the same way, the very elderly must be given particular therapeutic aid. If the authors of the drug prescription report question that, then their seriousness must be called into doubt.

The alternative to medical expectoration proposed in the drug prescription report, “simple fluid intake for adequate hydration,” was considered by Hofmann to be largely ineffective. As he emphasised, hyperhydration has never been shown to result in secretolysis in children, although diuresis and vomiting are to be expected. “To want to recommend to a small child suffering from chronic bronchitis and coughing day and night that it should take copious liquids and wait until the coughing has stopped can only be described as cynical”, the paediatrician declared.

CONSEQUENCE OF THE RECOMMENDATION: HIGHER SUBSEQUENT COSTS

As Hofmann explained, the consequences of this limitation on treatment and drugs are clearly apparent, ranging from prolonged disease duration, through intensification of the infection, to the increased occurrence of pneumonia with the need for in-patient treatment. Without doubt, antibiotic treatments and hospital admissions have an increasing effect on costs and thus contradict the original intention.

The mental stress on children and parents and the unnecessary suffering of elderly and multimorbid patients also come down on the negative side of the equation in respect of these recommendations, Hofmann pointed out.

SPECIAL EXTRACT FROM IVY LEAVES WITH CLEAR EVIDENCE OF ACTION

Dried ivy leaf extract (Prospan), a plant bronchospasmolytic, has been used successfully for almost 50 years in diseases with pathological secretion formation and impaired secretion transport, such as bronchitis and chronic obstructive airways diseases. Its content of glycosidic saponins, flavonoids and rutin causes a spasmolytic and secretolytic effect. The efficacy and safety of dried ivy leaf extract was confirmed in 1988 by the BGA in a positive-list monograph. Through its decision to license Prospan bronchial drops in July 1996, the BfArM (Federal Institute for Drugs and Medicinal Products) tested and confirmed this phytotherapeutic product in accordance with current strict criteria.

TO SUM UP

Dr. A. Gulyas: "Spirometric measurements showed a clinically relevant and significant improvement in ventilatory disorders with both dosage forms of the ivy leaf extract tested."

VARIOUS DOSAGE FORMS AVAILABLE

The stated efficacy in the monograph for Prospan drops has been clearly documented in controlled clinical studies. At the same time it was shown that dried ivy leaf extract in the new presentations of cough syrup for children and suppositories is equally effective and well tolerated.

As *Dr. H. Höhre*, Davos, explained, no pharmacokinetic studies are possible because of the numerous constituents of dried ivy leaf extract, so that conclusions as to the pharmacodynamic effects of different presentations can be better obtained in clinical equivalence studies. In the paediatric pneumology department of the Davos Wolfgang alpine hospital, the therapeutic equivalence of Prospan bronchial drops and suppositories for children was demonstrated using body plethysmographic measurement data in a 3-day treatment in 26 children with chronic obstructive airways disease. The children, aged 5 – 11 years, showed an at least 10% increase in forced expiratory volume in 1 second after inhalation of 200 µg fenoterol.

The secretolytic and bronchospasmodic effect of dried ivy leaf extract in the different pharmaceutical forms was quantified and shown to be statistically significant using measurements of various pulmonary function parameters. A marked reduction in bronchial obstruction was shown. Compared with the initial value, the measurements of pulmonary function on the first and third day of treatment, 3 hours after administration, showed a clinically relevant and significant increase in forced expiratory volume in 1 second. With Prospan suppositories for children, FEV1 increased on days 1 and 3 of treatment by 12.6% and 19.7%, respectively (Fig. 1). These values were comparable with the increase following treatment with Prospan drops (15.2% and 15.8%), explained Höhre.

The measurement of airways resistance by body plethysmography on the third day of treatment also showed a comparable, clinically relevant and statistically significant improvement 3 hours after administration of the corresponding drug compared with the measurement before administration. Raw decreased with the suppositories from 0.71 to 0.49 kPa/l/s and during treatment with the drops from 0.79 to 0.44 kPa/l/s.

The results of the study underline the fact that both Prospan suppositories for children and Prospan drops result in a marked improvement in ventilatory disorders on the basis of their secretolytic and bronchospasmolytic effect and in so doing are well tolerated, summarised Höhre. At the same time he pointed out that, because of the different absorption conditions for the equipotent suppositories, approximately 4 times the dosage of extract were necessary compared with administration of Prospan drops. The addition of ethanol to the drop preparation resulted in markedly better bioavailability.

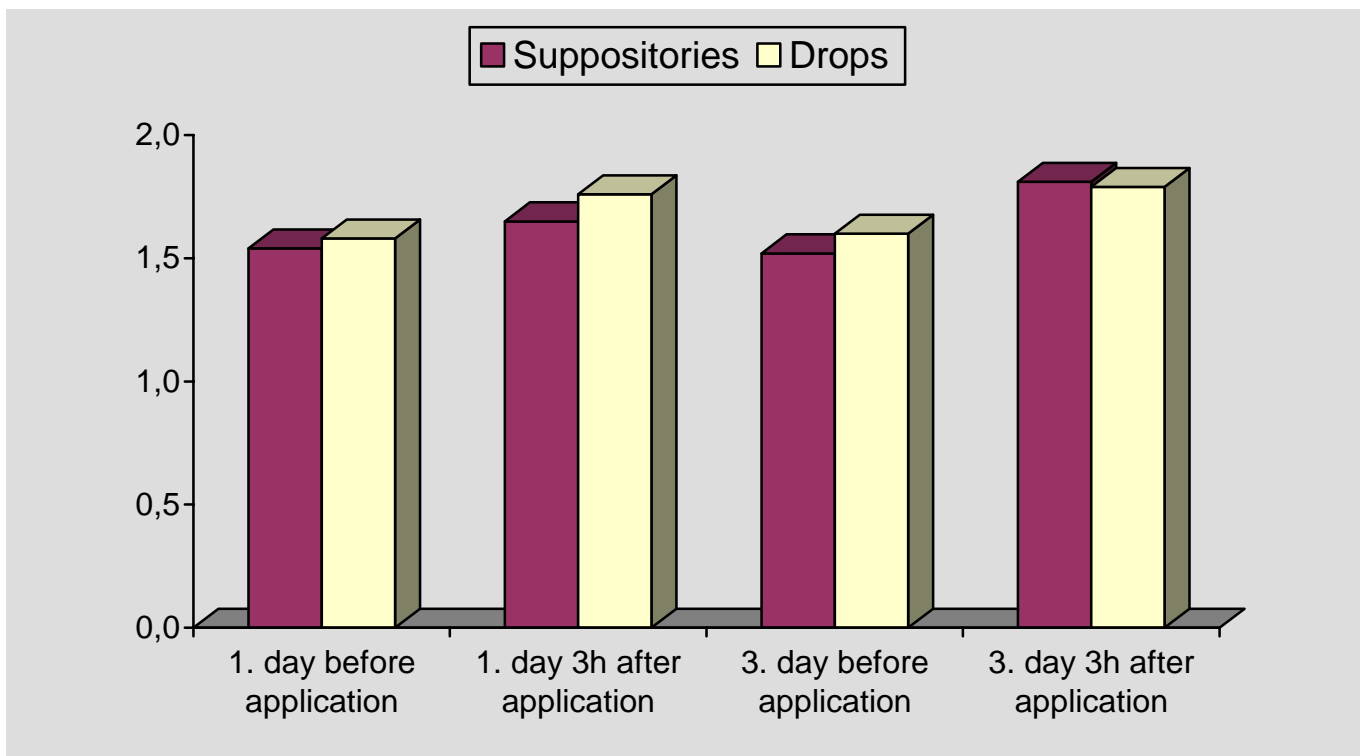


Fig. 1: Increase in forced expiratory volume in 1 second (FEV1) during therapy with Prospan suppositories for children and Prospan drops (For details of description see p.3)

ASTHMATIC CHILDREN BENEFIT FROM IVY LEAF EXTRACT

As Prof. Hofmann explained, according to recent findings the pathophysiology of bronchial asthma is characterised by chronic inflammation of the airways, in the pathogenesis of which eosinophilic granulocytes and, in the case of severe asthma, T-lymphocytes also play an essential role. Recurrent obstruction with dyspnoea, wheezing and asthmatic coughing are the predominant clinical signs of asthma. The inflammatory

reactions of the bronchial wall can easily lead to a lifelong, chronic condition. The symptomatic treatment of these chronic obstructive airways diseases therefore comes within the area of indications of dried ivy leaf extract, according to Hofmann.

The efficacy of a special dried ivy leaf extract in bronchial asthma and the therapeutic equivalence of Prospan drops and cough syrup for children was confirmed in a double-blind cross-over study in the Santa Maria specialist allergology clinic in Oberjoch. Spirometric measurements in 25 children aged from 10 to 15 years with bronchial asthma showed a clinically relevant and significant improvement in ventilatory disorders with both presentations of ivy leaf extract tested, reported *Dr. A. Gulyas*, Oberjoch. In addition, body plethysmographic measurements were taken and the objective data from these, irrespective of the patient's co-operation, correlated markedly with the spirometry results as well as confirming a significant reduction in bronchial obstruction.

The airways resistance improved on administration of the cough syrup from 3.77 before therapy to 3.39 kPa/l/s on day 10 of therapy, 3 hours after administration, and with Prospan drops from 3.74 to 3.39 kPa/l/s. The forced expiratory volume in 1 second increased after 10 days of treatment with the cough syrup for children from 2.01 to 2.15 l (and with the drops from 2.00 to 2.15 l). Once again it should be noted that with administration of the cough syrup a two-fold higher dose of extract was necessary for therapeutic equivalence with the ethanolic drops, Gulyas pointed out. Of particular note in the new study results on Prospan was the observation that the quantified improvements in bronchial obstruction exceeded the usual scale with secretolytic therapy. The anti-obstructive effect of ivy leaf extract was of an order of magnitude which otherwise is found with strongly active bronchospasmolytics such as β -sympathomimetics, Hofmann pointed out. "Three hours after Prospan medication, the bronchospasmolytic effect almost reaches the same order of magnitude as the inhalation of 2 puffs of fenoterol after 10 minutes. However, when comparing the side-effects, a markedly more favourable effect/side-effect profile can be observed for the ivy leaf extract," said Hofmann.

On the basis of its proven efficacy and not least also because of its good tolerability, the phytotherapeutic agent Prospan represents a rational therapeutic approach in the treatment of acute and chronic obstructive airways disease in children, the experts considered. Their demand was for the prescription of expectorants in future to be based on the documented efficacy of individual substances.

Press conference "Expectorants – disputed drugs? – Decision-making criteria for the doctor, Way out for patients". Frankfurt, 12 December 1996. Organiser: Engelhard Arzneimittel.

Author: Dagmar Jäger-Becker

INTERVIEW

Prof. D. Hofmann, Head of the General Paediatric Medicine Department, J. W. Goethe University Frankfurt, spoke in an interview about his personal views on the current situation.

? How common are acute and chronic bronchial conditions in childhood?

! Acute bronchial conditions are extremely common in childhood. The clinical picture of common acute bronchitis in childhood is presented on average 2 – 3 times annually. This statement, however, applies only if one includes pharyngitides which are not always clearly defined diagnostically. According to more recent statistics, chronic bronchial disorders such as bronchial asthma occur in about 8% of all school-age children. In babies and infants, the clinical picture of obstructive bronchitis is considerably more common. It appears clinically to be bronchial asthma, but frequently disappears after infancy. Up to 25% of all children are affected.

? Can the reflex liquefaction of secretion, which is effectively the principle of ivy leaf extract therapy, also be replaced by increased liquid intake?

! Reduced liquid intake undoubtedly results in thickening of bronchial secretions and hence impaired expectoration. Increased liquid intake over and above normal hydration, however, has no documented effect on bronchial secretions. All that may be expected from this is diuresis. Thus, the principles of action of expectorants cannot be replaced by increased liquid intake.

? In which clinical pictures do you see indications for expectorants? When is a bronchospasmolytic effect additionally necessary?

! Indications for treatment with expectorants include common acute bronchitis, frequently recurring bronchitis and, in particular, all forms of obstructive bronchitis and infectious asthma. In this last group, an additional spasmolytic effect is urgently necessary to maintain a bronchomotor, and hence a secretion-limiting, effect in addition to improving bronchial tone.

• *What consequences will this “negative recommendation” have for general practitioners and paediatricians? What can you recommend to your colleagues out there in clinical practice in the present situation?*

! In the first place, the recommendation not to prescribe expectorants on a panel prescription has resulted in great uncertainty among office-based general practitioners and paediatricians. If a drug which has been used for decades and which is established in clinical practice is suddenly no longer supposed to be effective, one doubts one's own capacity for observation and one's critical approach to drug therapy. For this reason I can only advise office-based colleagues to continue the treatment unchanged, admittedly strictly indicated, but at the least in all forms of bronchitis with obstruction and in protracted bronchitis, as well as in the condition of frequently recurring bronchitis.

Interviewer: Dagmar Jäger-Becker