

The role of hyposensitization: do we need to start rethinking?

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Abbreviation

ETAC Early Treatment of the Atopic Child study

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The fact that allergies are on the rise, in their frequency and possibly also in the multitude of manifestations and the severity of the individual symptoms, has been established by the media and therefore is well known by the public. It has also become common knowledge that allergies are more widespread in the industrialized nations of the West than, for example, in the Third World or in the former socialist block countries. In the eastern German states, as well as in countries such as Estonia, which are even more strongly shaped by a rural way of life, the disappearance of the borders and the adoption of Western habits has led to a rapid increase in the prevalence of allergic disorders without us really knowing the causes of this development. Furthermore, the fact that the age-based prevalence of allergic disorders continues to climb even in Germany, as shown in a recent article from Münster [1], is surprising. In this paper the prevalence of hay fever in 13-year-old school children rose within 5 years from 22.7% to 24.7% for boys and from 19% to 22.3% for girls. The case for asthma and eczema appears to be similar, which prompted the editors of the European journal *Allergy* to state in an editorial that approximately every fourth child in Europe suffers from allergies and we do not know what tomorrow brings [2*].

At the same time, there have been many attempts at prevention. A Danish investigation has just been published which shows that 132 studies alone have dealt with the topic of breastfeeding and allergies [3]. Looking at it as a whole, breastfeeding appears to be beneficial especially for infants with an atopic family history. If one attempts, however, to use other elementary preventive measures, a much more inconsistent picture presents itself. Adnan Custovic from Manchester recently summarized the results of various prevention studies and

presented them at the meeting of the European Society of Allergologists in Paris [4**]. While in some of these birth cohorts allergen elimination in infancy seemed to be advantageous, in others a negative effect was shown. On examining the highly controversial topic of pet-keeping in particular, the various studies are quite contradictory. What applies to the primary prevention of sensitization appears much more convincing for the secondary prevention of subsequent allergic disorders. Surprisingly, the clearest results were not found in plain prevention studies, but rather in studies in which medicinal prevention strategies were investigated. The same is true for the already classic subgroup analysis by the ETAC (Early Treatment of the Atopic Child) study [5], but even more so for studies in which hyposensitization was applied. In the ETAC study, it was shown that in children with atopic dermatitis who were also sensitized to grass pollen or house dust mites after their first birthday, the probability of developing asthma was significantly reduced if the children had been treated with 5 mg of cetirizine for 18 months between their first and second birthdays. Interestingly enough, the protective effect of the 18-month medicinal treatment also lasted for the next 18 months, when the children were not treated with antihistamines. A subsequent study that focuses solely on this combination (atopic dermatitis and sensitization to airborne allergens) aims to prove the reproducibility of the results. However, the results of the PAT study [6*] were even clearer. In this study, 208 school children aged 6–14 years who suffered from allergic rhinoconjunctivitis underwent hyposensitization for 3 years. Not only could a distinct reduction in the symptoms caused by the disorder be observed, but also significantly fewer occurrences of bronchial hyperreactivity were noted at the end of the observation period. The results of a subsequent study examining 142 of these children have been published 2 years after completing treatment. It has been shown that the advantageous effects of the 3-year hyposensitization remain intact in the long term as well. The development of new sensitizations can also be reduced by specific immunotherapy.

Yet, the studies leave several questions unanswered:

- (1) whether hyposensitization as discussed in the studies can be administered subcutaneously or orally;
- (2) how quickly an effect sets in;
- (3) how long the protective effect lasts after sublingual therapy is stopped.

Interesting studies dealing with these topics have been published within the last few months that may require us to rethink our treatment recommendations.

The efficacy of sublingual hyposensitization in allergic rhinitis: a Cochrane review

This Cochrane review [7•] deals with the question of whether the symptoms of allergic rhinoconjunctivitis can be relieved by sublingual hyposensitization and whether the intake of symptomatic medication can be reduced. Up to September 2002, 22 clinical studies involving the application of sublingual therapy had been published in recognized English language journals. All of these investigations were double-blind, placebo-controlled, parallel-group studies to which no methodological objections could be made. The majority of these studies, in which a total of 979 patients participated, were performed in adults; however, there were four studies in which only children were treated. On average, a highly significant reduction in symptoms could be noted, in most cases as early as after one treatment cycle, as well as a definite decrease in medicine intake for symptoms. The results for seasonal allergens were more convincing than those for perennial allergens, although it is possible that the latter yielded no statistically significant results due to the low case number. The same applies for the treatment of children, the actual domain of sublingual therapy. Here again, the statistical significance was not confirmed, which is no surprise considering only 152 cases were observed. A question that this very comprehensive analysis could not answer, however, was whether sublingual therapy equals the efficacy of injection treatment. Adequate comparative investigations have only now been published, and they demonstrate comparable efficacy [8,9].

Onset of action and tolerability of sublingual ultra-rush hyposensitization

At this year's meeting of the European Allergologists, Hans F. Merk reported on an interesting clinical investigation [10]. In this investigation, 107 patients with seasonal symptoms of allergic rhinitis were up-titrated in four steps to the sublingual maintenance dose of 300 IR within 90 min. Nearly every second patient reported experiencing side effects during this procedure; these, however, were mild to tolerable and delayed reaching the maintenance dose by 1 day in only two patients. One single patient dropped out of the study because of gastrointestinal discomfort. Several studies investigating such ultra-rush schemes were presented by other renowned hospitals at the same meeting. Their good tolerability and immediately occurring immunological effects were noted, which are also reflected in clinical effects. The most convincing example of one such study comes from the Allergological University Hospital in Marseille [11]. There it was proven that such an ultra-rush concept begun during the season does not

differ in its efficacy from a combined administration of loratadine tablets and triamcinolone nasal spray. Due to its immediate onset, hyposensitization has thus become an alternative in the treatment of symptomatic allergic patients. A total of 29 studies on sublingual hyposensitization from virtually all the European countries were presented at this year's European Allergologists Conference. This impressively proves that a process of rethinking has begun.

The long-term effect of sublingual hyposensitization

At the annual meeting of the American Academy for Allergy, Asthma and Clinical Immunology, Giovanni Passalacqua [12] presented the results of a long-term investigation into sublingual hyposensitization. In this randomized, controlled study in patients allergic to mites, 35 school children were treated with sublingual hyposensitization for 4–5 years, while another 25 children were treated solely for symptoms. At the end of the treatment phase – interestingly, 4–5 years after finishing treatment, too – a clear and statistically significant reduction in asthma symptoms as well as the required asthma medication could be found in patients treated with hyposensitization in comparison with the control group.

We need to rethink

The recommendations made by the WHO for the treatment of allergic rhinitis and for the prevention of asthma [13] correspond to a large extent to the recommendations of the European Academy of Allergy and Clinical Immunology published in the year 2000. Treatment with antihistamines is always in the foreground, and if necessary is accompanied by nasal steroids when nasal symptoms predominate. Allergen avoidance is required whenever possible. Not until later stages of the disorder should hyposensitization be applied, according to the recommendations of the WHO. At the same time, the dangers of the use of (subcutaneous) hyposensitization schedules are highlighted. Current health policies would be only too willing to follow these recommendations, since several years ago antihistamines and nasal steroids became available as generic and over-the-counter products. Yet, is it not disastrous to leave a rapidly spreading disorder, which already affects one in four schoolchildren, up to self-medication by the patient – a disease that in many cases has been proven to be the beginning for asthma and sinusitis? Furthermore, we have recent and strong evidence that

- (1) hyposensitization prevents asthma;
- (2) sublingual hyposensitization is safe in its application;
- (3) sublingual hyposensitization is effective and tolerable;
- (4) the effect begins soon after titration.

The recommendations made by the WHO are only 2 years old, however in their core they are once again outdated. According to the current state of scientific knowledge, hyposensitization should be our first line treatment, and it can be administered sublingually, especially in children. It is necessary to come to an agreement quickly, only then can the increase in subsequent diseases such as asthma and sinusitis be limited. An interesting research topic is still left for science to explain: the reason for the mysterious rise in allergies.

References and recommended reading

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