A randomized equivalence trial comparing the efficacy and safety of Luffa-comp.-Heel Nasal spray with Cromolyn sodium spray in the treatment of seasonal allergic rhinitis.

Michael Weiser, Lutz H. Gegenheimer, Peter Klein
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SUMMARY

Background: The objective of the clinical study was to investigate the efficacy and tolerance of a homeopathic nasal spray in cases of hay fever (seasonal allergic rhinitis) in comparison with the conventional intranasal cromolyn sodium therapy. **Patients and methods:** In total 146 out-patients with symptoms of hay fever were enrolled into the clinical study (randomized, double-blind, equivalence trial) (time of treatment: 42 days). The homeopathic remedy Luffa comp.-Heel™ Nasal Spray, dosage: 0.14 ml per application, 4 times a day in each nostril consisted of a fixed combination made up of Luffa operculata, Galphimia glauca, Histaminum, and Sulfur. The main outcome measure of the efficacy was the quality of life as measured by means of the Rhinoconjunctivitis Quality of Life-Questionnaire (RQLQ). The tolerance of the trial medication was registered by means of global assessment, rhinoscopy, recording of adverse events and with the aid of vital and laboratory parameters. **Results:** The results of the study demonstrated a quick and lasting effect of the treatment. This effect was independent from the medication applied and produced a nearly complete remission of the hay fever symptoms. The RQLQ global score changed significantly in the course of the treatment, indicating therapeutic equivalence between the two forms of treatment. Adverse systemic effects did not occur. Local adverse events appeared in three patients. **Conclusions:** The study proved that, for the treatment of hay fever, the homeopathic nasal spray is as efficient and well tolerable as the conventional therapy with cromolyn sodium.

INTRODUCTION

Seasonal allergic rhinitis (hay fever) is widespread among the general population. The prevalence of the disease in Central Europe is estimated to range around 20% [1,2]. Seasonal allergic rhinitis is provoked by pollen from various plants. Via an immunological mechanism they cause inflammation of the nasal mucosa which is associated with characteristic symptoms including nasal hypersecretion and obstruction, mucosal erythema and edema, sneezing, and itchy nose. Accompanying symptoms of allergic conjunctivitis, fatigue, and headache may in addition impair subjective well-being. The intensity of these symptoms depends on the extent of antigen exposure and is thus season-specific. Concentrations of tree pollens are generally highest in spring, while grass pollens are more abundant in summer and weed pollens in late summer and early autumn [3].

Since pollen allergens are ubiquitous and difficult to avoid, and since desensitization may take years, is not always successful, and carries risks (e.g. anaphylaxis), symptomatic treatment of hay fever is often necessary. Conventional medicine offers several well-established therapeutic strategies, such as intranasal cromolyn sodium, intranasal or oral antihistamines as well as intranasal and, if necessary, oral corticosteroids.

A homeopathic remedy for seasonal allergic rhinitis was developed as a therapeutic option comprised of Luffa operculata, Galphimia glauca, Histaminum, and Sulfur.

The constituents of this remedy (manufactured and marketed as Luffa comp.-Heel™ (Nasal Spray, by Heel GmbH, Baden-Baden, Germany) have accordingly been coordinated in such a manner that they effectively complement each other in their therapeutic action: Galphimia glauca and Histaminum are two agents whose therapeutic effectiveness is well known, especially for affections of the skin and mucous membranes. Their therapeutic action is enhanced by sulfur as a stimulation (reversal) remedy for chronic and inflammatory diseases, and Luffa operculata, indicated for common colds and allergic affections of the respiratory organs such as hay fever and asthma. The homeopathic nasal spray used in this study contains a fixed combination of Luffa operculata and Galphimia glauca in dilutions D4, D12, and D30 and Histaminum and Sulfur in dilutions D12, D30, and D200 (the degree of dilution is indicated by an X, which indicates the ratio of 1 part of active ingredient to 9 parts of diluent. A "D1" indicates a ratio of 1:10, a "D2" indicates a dilution of 1:100, etc. [4,5]). In a meta-analysis of seven randomized double-blind trials Galphimia glauca proved superior to placebo in reducing ocular hay fever symptoms; the response rates of Galphimia glauca were estimated to be similar to those specified for conventional antihistamines [6]. The present study was designed to compare Luffa comp.-Heel™ Nasal Spray with a nasal spray containing 20 mg/ml cromolyn sodium (usual concentration marketed in Germany) with respect to both efficacy and tolerance in the therapy of seasonal allergic rhinitis.

PATIENTS AND METHODS

The study protocol was approved by an independent Ethics Committee and implemented in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. All patients participating in the study gave written informed consent. The study was performed according to a parallel group design. Within each study center the patients were evenly randomized to cromolyn sodium or homeopathic treatment (because the number of patients recruited by each center could not be estimated a priori, randomization was performed in blocks of 2). In a double-blind manner, one spray, about 0.14 ml, was administered 4 times daily into each nostril. During acute exacerbation of symptoms, up to 8 sprays per nostril were allowed. To ensure blinded conditions both compounds (representing aqueous solutions and containing benzalkonium chloride as a preservative) were dispensed in identical, neutral bottles (possibly by direct and immediate comparison the preparations were distinguishable by taste). Sealed envelopes containing the code for each patient were supplied by the sponsor to the investigators. Only in cases of emergency was it permitted to break the individual random code (the code was broken after data entry and after decision-making about protocol deviations/evaluation groups through the responsible biostatistician).

Patients were recruited from different study centers located in the same geographic region (Upper Rhine Valley of Germany) during the hay fever seasons of 1996 and 1997. They were to be seen for assessment of baseline status (visit 1), and after 7±1, 14±2, 28±3 and 42±3 consecutive days of treatment (visits 2 to 5). The treatment duration of 6 weeks was chosen based on clinical experience; it was short enough to ensure that in the majority of patients antigenic exposure persisted throughout their participation in the trial, and long enough to compensate for variation of weather conditions affecting pollen concentrations.

STUDY POPULATION

Male and female outpatients, aged 18 to 60 years, suffering from seasonal allergic rhinitis as diagnosed by RAST (IgE-antibody measurement), scratch or skin-prick test were eligible for the study. Patients were excluded if they had a diagnosis of perennial allergic rhinitis or infectious diseases of the upper respiratory tract; known hypersensitivity to the study medication; treatment with drugs containing cromolyn sodium or corticosteroids within two weeks of the study start; treatment with antihistamines or alpha-sympathomimetics within 24 hours of the study start; or regular use of anti-inflammatory agents and analgesics. No pregnant or nursing women were accepted. In addition, to reduce the risk of dropouts due to the need for prohibited co-medication, patients were disqualified from study participation if they had a history of emergency treatment of allergic symptoms or of regular treatment of hay fever with oral corticosteroids and/or antihistamines during the past two years (by this restriction an overrepresentation of patients suffering from mild to moderate symptoms was favored). Prohibited co-medication encompassed any compounds used for treatment of hay fever (even if they were not prescribed for this indication) other than the respective study drug (in particular: alpha-sympathomimetics, corticosteriods and antihistamines); this also applied to the therapy of ocular hay fever symptoms.

ASSESSMENTS

Drug efficacy was assessed primarily with a validated self-rating (patient) instrument, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [7,8]. The German adaptation of the questionnaire [9] was completed at visits 1 through 5. The questionnaire consists of 28 items that pertain to particular symptoms and their practical consequences for daily life. The items are subdivided into seven domains: 1) nasal symptoms (4 items); 2) ocular symptoms (4 items); 3) general non-hay fever symptoms (7 items); 4) sleep disturbances (3 items); 5) practical problems associated with rhinoconjunctivitis, such as carrying tissues and nose blowing (3 items); 6) implications on 3 personal activities named by the patient at the outset (3 items); and 7) emotional symptoms, such as frustration (4 items). The particular items are represented by questions of the general form 'how troubled have you been by (e.g. stuffy nose)' that refer to the preceding week. Patients rated the degree (physical symptoms and their practical implications) or the temporal extension (emotional symptoms) of their subjective impairment on a 7-point scale ranging from 0 (not troubled at all; none of the time) to 6 (extremely troublesome; all the time). Domain-specific scores were obtained by averaging the numerical values of the pertinent items. Division of the sum of the domain-specific scores by the number of domains yielded an overall score reflecting the quality of life of patients suffering from seasonal allergic rhinitis. This overall score, ranging from 0 to 6 (highest to lowest quality) was the main efficacy parameter.

In addition, efficacy was measured by using the domain-specific subscores and the global assessment of the present quality of life on a visual analog scale that ranged from 0 mm ("could not be worse") to 100 mm ("could not be better") at visits 1 through 5. The global assessment of therapeutic efficacy at the end of treatment was measured by both patient and investigator on a 4-point scale ranging from "excellent" to "poor".

Local tolerance was assessed at visits 2 through 5 by rhinoscopic examination (using a nasal speculum) of the nasal mucosa for erythema, edema, and dryness of nose. These symptoms were classified on a 5-point scale ranging from "missing" to "strong." Patients also rated nasal pruritus, urge of sneezing, and feelings of burning and dryness of nose on 5-category scales according to frequency (from "never" to "after each administration") and intensity (from "slight" to "very strong").

At the end of treatment, tolerance was globally assessed by both the patient and the investigator on a 4-point scale ranging from 1 (very good) to 4 (poor). Physicians performed drug safety evaluations based on the incidence of adverse events reported at visits 2 through 5, and monitoring of vital signs and laboratory status, such as hematology, clinical chemistry, and urinalysis, at visits 1 and 5.

STATISTICAL EVALUATION

To show the non-inferiority of the homeopathic group according to the "Statistical Principles of Clinical Trials" a one-sided -(1-α) confidence interval (CI) was used. Equivalence was inferred if the lower limit of the interval was larger than the equivalence limit. For the main efficacy parameter (overall RQLQ scores at visits 2 through 5) a generalized Wilcoxon-Mann-Whitney procedure was used (directional test for stochastic ordered alternatives according to Wei and Lachin) (10-12). A one-sided equivalence test can be formulated using the Mann-Whitney statistic $P(X<Y)+0.5P(X=Y)$ [abbreviated as $P(X<Y)$]. It is a measure of stochastic superiority. Values lower than 0.5 denote inferiority and values higher than 0.5 denote superiority. The test for one-sided equivalence ("equivalent" or "better") can be performed by means of a one-sided (1-α) CI in the following way: if the lower bound of the CI is larger than 0.36 (corresponding to a medium-sized inferiority according to Cohen [13]), the null hypothesis of inferiority can be rejected (null hypothesis H0: $P(X<Y)(0.36$; alternative hypothesis HA: $P(X<Y)>0.36$).

The analysis of all randomized patients may be biased toward demonstrating equivalence. For this reason the first-line analysis for efficacy was a per-protocol analysis considering dropout rates and major study protocol deviations. Missing values because of dropouts were replaced using the principle of "last value carried forward". None of the patients excluded from per-protocol analysis had an observation after medication. Therefore an additional intention-to-treat analysis was not performed. Demographic data and baseline characteristics were analyzed by means of Mann-Whitney´s U-test and Fisher's exact test.

Domain-specific RQLQ scores, visual analog scores, results of global assessment of therapeutic efficacy, and tolerance ratings performed by patients and investigators were analyzed by means of explorative methods based on Mann-Whitney statistics and pertinent 95% CI. An analysis of homogeneity of efficacy data across study centers was performed by providing an overview of treatment effects by mean scores. Because there was no evidence of interaction between centers and treatment no supportive analysis was done.

SAMPLE SIZE CALCULATION

At the time the study was designed (1995) there was no sample algorithm available for the test to be used. Thus, an appropriate procedure was used: t test one-sided with the analog difference, which was a standardized difference of 0.5. When the sample size in each group is 72, a two group 0.05 one-sided t test will have 91% power to reject the null hypothesis that the test and standard are not equivalent (the difference in means is 0.5 or farther from zero in the same direction) in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.0 and the common standard deviation is 1.0.

RESULTS

Demographic and Baseline Characteristics

A total of 146 patients (82 male, 64 female) recruited from 17 centers (each contributing 1-25 cases), including 10 general practitioners, 5 ear-nose-throat physicians and 2 internists in private practice, were enrolled in the study. From this population 72 patients were randomly assigned to the homeopathic group and 74 to the cromolyn sodium group. A total of 135 patients (68 in the homeopathic, 67 in the cromolyn sodium group) completed the trial according to protocol. Seven patients dropped out after visit 2 (2 patients in either group due to end of pollen season; one from the homeopathic and 2 from the cromolyn sodium group due to lack of efficacy/wish of patient/or other reasons). They were included in the analysis of efficacy, whereas 4 other patients could not be included because they dropped out before visit 2 (one of the cromolyn sodium group due to adverse events and 2 from the cromolyn sodium group and one from the homeopathic group due to lack of efficacy/wish of patient/other reasons) (fig. 1).

FIGURE 1 **Study profile**

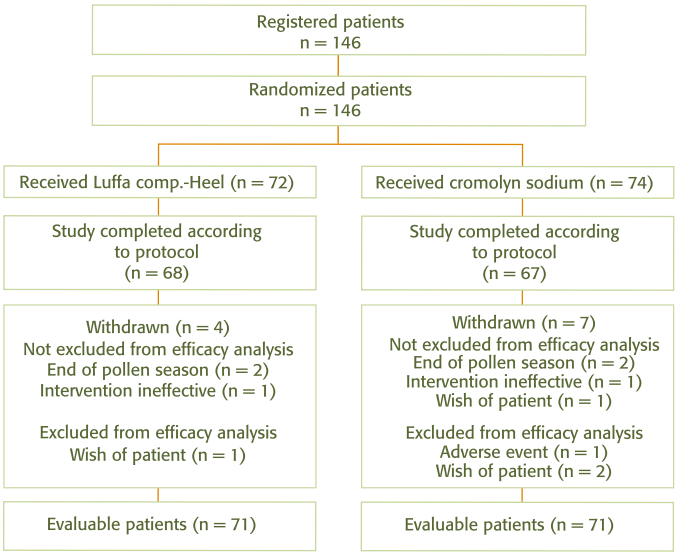


TABLE 1

Demographic and baseline characteristics of total population by treatment group

Parameter[1]	Homeopathic group	Cromolyn sodium group
Number of patients enrolled	72	74
Number of males/females	44/28	38/36
Mean age ± SD (years)	36.8 ± 9.6	34.7 ± 11.6
Mean height ± SD (cm)	171.5 ± 9.3	172.3 ± 7.7
Mean weight ± SD (kg)	70.7 ± 15.8	68.7 ± 11.6
Mean overall RQLQ score at visit 1 ± SD	2.41 ± 1.09	2.37 ± 1.14

[1] SD = standard deviation

Demographic characteristics of the total study population are summarized in table 1. There were no statistically significant differences between the two treatment groups with respect to sex, age, height, weight. The same applies to the overall RQLQ score at visit 1 which averaged 2.37 in the cromolyn sodium group and 2.41 in the homeopathic group (but individually reached up to 4.7 and 4.9, respectively, thus indicating that higher baseline scores were disfavored in this study but not excluded). Comparability can also be assumed for the essential anamnestic parameters (table 2). In only 4 of the enrolled patients hay fever was newly diagnosed; the others had suffered from one or more previous episodes of the disease (mean duration of medical history: 9.3 years in the homeopathic group and 7.2 years in the cromolyn sodium group), most of them for 1-6 months during spring and/or summer. In the 51 patients of either group for which they were documented, the provoking allergen(s) was (were) tree pollens (mostly hazel, birch, alder, ash), alone or in combination with grass or weed pollens (such as mugwort and rye), without notable group-specific differences.

Since the patients lived in the same geographic region it can be concluded that the patients and thus the treatment groups were simultaneously exposed to roughly the same pollen types and concentrations (fig. 2). In both groups the beginning of treatment was similarly distributed to the months of the year (between February and August with an accumulation in spring). Equivalence considerations can therefore be carried out disregarding environmental and predispositional conditions.

An influence of concomitant medication (which was used by 16 patients in the homeopathic group and 12 patients in the cromolyn sodium group) on the study results did not become evident. The average compliance with the administration of the two study drugs (93% in the homeopathic group and 98% in the cromolyn sodium group) was comparable.

TABLE 2:

Allergy-specific anamnestic data of patients included in efficacy evaluation by treatment group

Parameter[1]	Homeopathic group n	Homeopathic group duration[a]	Cromolyn sodium group n	Cromolyn sodium group duration[a]
Past occurrence of hay fever				
No	3	--	1	--
Yes[b]	64	9.3 ± 8.6	69	(7.2 ± 6.6)
Yes	4		1	
	(unknown)		(unknown)	
Allergen(s) documented	51		51	
- tree pollen/grass or weed pollen	20/12		25/12	
- tree and grass or weed pollen	18		13	
- not classified	1		1	
- not documented	20		20	
Season of past occurrence of hay fever[c]				
- spring	47		52	
- early summer/summer	41/18		43/14	
- late summer/autumn	5/2		6/0	
Duration of hay fever in past years				
- < 1/1-2 month(s)	4/14		2/16	
- 2-3/3-5 months	13/13		9/13	
- > 5 months/unknown	7/20		8/23	
Past desensitization	7		6	
Environment of residence				
- rural/urban	41/30		36/35	

[a] Years (mean ± SD) [b] Duration of individual history before enrolment. [c] Patients could be assigned to more than one category.

EFFICACY

Data from a total of 142 patients (71 homeopathic and 71 cromolyn sodium) were subjected to efficacy analysis. Figure 3, which illustrates the time course of the mean overall RQLQ score from visit 1 to visit 5, reveals a marked reduction of subjective impairment in both treatment groups, starting from nearly equal baseline levels. The decrease of the primary parameter was slightly more pronounced in the cromolyn sodium group (from 2.37 to 1.33) than in the homeopathic group (from 2.41 to 1.57). Under both treatments, the effect was most striking during the first week. The alternative hypothesis (therapeutic non-inferiority of homeopathic versus cromolyn sodium treatment), with α=0.05, with the chosen equivalence bound P(X<Y)=0.36 is confirmed. The Mann-Whitney statistic for the combined (directional) test of this study was P(X<Y)=0.44, showing the homeopathic group to be slightly inferior. However, the lower bound (LB) of the confidence interval was 0.37 which is above the equivalence bound of 0.36. Thus, equivalence (efficacy) of the homeopathic treatment could be proven.

All RQLQ subscore means showed time courses similar to that of the overall score. Mean baseline subscores ranged from 3.34 to 1.53 and mean final scores from 1.93 to 0.99. The most marked reductions, amounting to 1.2 - 1.6 points, were related to nasal symptoms, practical problems, and individual activities (table 3).

The results of the visual analogue scores were in accordance with the RQLQ scores, indicating that the perceived quality of life increased during the study. Between visit 1 and visit 5, the visual analogue scores of the homeopathic group increased by 24% (from 55 to 68 mm) and those of the cromolyn sodium group increased by 29% (from 57 to 74 mm) (Visit 1: U test P=0.72, P(X<Y)=0.47, 95% CI LB=0.38; Visit 5: U test P=0.92, P(X<Y)=0.43, 95% CI LB=0.35).

Global assessments of therapeutic efficacy did not markedly differ with respect to treatments or the rating person. The therapeutic efficacy of the homeopathic treatment (vs. the cromolyn sodium treatment) was rated as "excellent" by 13% (vs. 24%) of the patients and by 16% (vs. 18%) of the investigators, as "good" by 63% (vs. 55%) and 63% (vs. 66%), respectively, as "satisfactory" by 18% (vs. 14%) and 17% (vs. 9%), respectively, and as "poor" by 6% (vs. 6%) and 4% (vs. 6%), respectively (patient assessment: U test P=0.92, P(X<Y)=0.44, 95% CI LB=0.37; investigator assessment: U-test P=0.82, P(X<Y)=0.46, 95% CI LB=0.39).

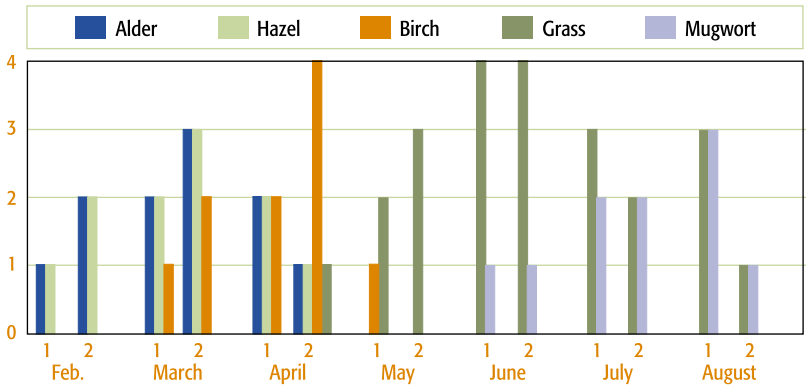


FIGURE 2

Classification of pollen exposure. Abscissa: 1 = first half of the month, 2 = second half of the month. The data are based on information form 'Deutscher Pollenflugwetterdienst' and were pooled for the years 1996/97: Ordinate: 1 = mild, 2 = moderate, 3 = severe, 4 = very severe

TABLE 3:

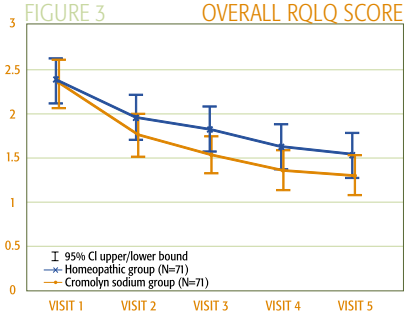
Mean ± SD values of RQLQ subscores at visit 1 and visit 5 (Mann-Whitney statistic P(X<Y), and pertinent lower 95% confidence bounds in parentheses

RQLQ Domains	Homeopathic group	Cromolyn sodium group	Statistics: P(X<Y) (95% CI LB)	Homeopathic group	Cromolyn sodium group	Statistics: P(X<Y) (95% CI LB)
Nasal symptoms	3.07 ± 1.31	3.25 ± 1.51	0.53 (0.45)	1.86 ± 1.42	1.7 ± 1.34	0.47 (0.39)
Ocular symptoms	1.87 ± 1.50	2.12 ± 1.53	0.55 (0.46)	1.26 ± 1.34	1.10 ± 0.98	0.50 (0.42)
Non-hay fever symptoms	1.99 ± 1.38	1.86 ± 1.37	0.47 (0.38)	1.44 ± 1.21	1.20 ± 0.98	0.45 (0.37)
Sleep disturbances	1.65 ± 1.29	1.53 ± 1.39	0.46 (0.38)	1.24 ± 1.18	1.08 ± 1.06	0.47 (0.39)
Practical problems	3.22 ± 1.67	3.27 ± 1.79	0.51 (0.42)	1.92 ± 1.62	1.69 ± 1.38	0.47 (0.39)
Individual activities	3.34 ± 1.45	2.87 ± 1.57	0.41 (0.32)	1.93 ± 1.55	1.58 ± 1.37	0.43 (0.35)
Emotional symptoms	1.76 ± 1.38	1.74 ± 1.17	0.51 (0.42)	1.37 ± 1.36	0.99 ± 0.95	0.44 (0.36)

TOLERANCE

Under both treatments, rhinoscopic assessments of erythema, edema, and dryness of the nasal mucosa remained largely unchanged during visits 2 through 5. In the cromolyn sodium group there was a sustained minor relief of all symptoms, whereas the ratings in the homeopathic group, also being consistently slightly better at the beginning than at the end of the observation period, were subjected to some intermediate fluctuation. Similar results occurred relative to patients' assessments of nasal pruritus, sneezing, and sensations of burning and dryness of the nose. All of these symptoms were rated as less intense and less frequent at visit 5 than at visit 2. The differences were small and comparable for both treatments.

FIGURE 3 OVERALL RQLQ SCORE



The tolerance of the homeopathic treatment (vs. the cromolyn sodium treatment) was assessed as "very good" by 25% (vs. 28%) of the patients and by 29% (vs. 31%) of the investigators; as "good" by 69% (vs. 61%) and 63% (vs. 58%), respectively; and as "satisfactory/poor" by 4% (vs. 5%) and 7% (vs. 5%), respectively. In general, the vast majority of investigators and patients had no complaints about tolerance (patient assessment: U test P=0.70, P(X<Y)=0.48, 95% CI LB=0.41; investigator assessment: U test P=0.63, P(X<Y)=0.48, 95% CI LB=0.40).

SAFETY

A total of four adverse events (observed in three patients) reported during the study were rated as "possibly," "probably," or "very probably" related to treatment. All were mild to moderate. Minor, intermittent nose bleeding occurred for two days after 30 days of homeopathic treatment. A sensation of burning in the nose, as well as discrete facial exanthema, occurred for 8 days after 1 day of homeopathic treatment. A sensation of burning in the nose, which caused the patient to drop out of the study, occurred after 5 days of cromolyn sodium treatment. All adverse events disappeared spontaneously; a premature revelation of the random code was not necessary. All clinically relevant laboratory values measured during the study resulted from concomitant or intervening diseases. Medians of hematology, clinical chemistry, urinalysis, and vital signs at visit 1 and visit 5 were consistent with normal values. There was no evidence of adverse systemic action for either the homeopathic or the cromolyn sodium treatment.

DISCUSSION

Topical cromolyn sodium is a well-established standard therapy for seasonal allergic rhinitis and conjunctivitis that proved superior to placebo in many clinical trials and has frequently been used as reference [14-20]. By this means it was possible to avoid the ethical problems arising from implementation of a placebo treatment in patients suffering from symptoms of considerable intensity. For the present study these problems would have been particularly relevant due to the long duration of 6 weeks. Moreover, to prevent a high dropout rate in a placebo group and yet to maintain double-blind conditions it would have been necessary to allow non-homeopathic rescue medication (e.g. a topical antihistamine) also to the patients of the homeopathic group; this, however, would have restricted the validity of the study results since the interaction of homeopathic and non-homeopathic medication cannot be evaluated. For the same reason the only rescue measure allowed in this trial was a short-term dose increase of the regular compound to which the particular patient had been randomized.

However, even in the absence of a placebo control, the study results strongly suggest that both treatments were in fact effective. About 70-80% of the total mean overall RQLQ score reduction occurred within the first two weeks of treatment in both groups. Because most patients were experienced hay fever sufferers who consulted physicians at an early stage of symptom development, it is likely that antigen exposure increased rather than decreased during the initial treatment period. From anamnestic data, we know that the majority of patients were sensitive to different antigens present during different periods so that their hay fever persisted for months. Moreover, only 4 patients dropped out due to end of pollen season (i.e. due to cessation of airborne pollen dissemination). It can therefore be assumed that antigenic exposure was maintained throughout the 6 weeks of treatment.

In their validation studies Zander *et al* [9] found a mean overall RQLQ score of 1.0 in a population of asymptomatic hay fever patients investigated during the winter; in a group of symptomatic patients completing the RQLQ during hay fever season they found a score of 3.0 before and a score of 1.5 after 14 days of antiallergic treatment. For the present study these results suggest two conclusions. First, at the end of both homeopathic and cromolyn sodium treatment the remission of hay fever symptoms and associated subjective impairment was largely complete. The final mean RQLQ scores of 1.57 for the homeopathic group and 1.33 for the cromolyn sodium group (which correspond fairly well to the post-treatment result of the validation study) are close to the putative minimum level, which likely could not have been reduced much further considering the persistence of antigen exposure. Second, the mean pre-treatment overall RQLQ score in the symptomatic groups of the studies by Zander *et al* [9] may have been more representative than the mean pre-treatment scores in the present study, in which participation depended on certain restrictions that disfavored the enrollment of patients with severe allergic reactions. Therefore, the statements about the efficacy of homeopathic and cromolyn sodium therapy may be particularly valid in cases of mild or moderate symptoms of seasonal allergic rhinitis that prevail in the general population.

Interestingly, the intensity of ocular symptoms in this study was reduced, according to the pertinent drop in RQLQ score, from 1.87 to 1.26 in the homeopathic group, and from 2.12 to 1.10 in the cromolyn sodium group, although only 6 patients in the homeopathic and 2 in the cromolyn sodium group used eye drops. This ocular relief has also been described in other studies [16,21] involving intranasal cromolyn sodium and antihistamines (and may therefore represent a general indicator of a successful therapy) and was not attributed to a systemic action but to an improved nasal drainage.

A recent meta-analysis showed that the clinical effects of homeopathy generally are due to more than a placebo effect [22], and in a study using an oral formulation of mixed grass pollens this was demonstrated for the therapy of hay fever in particular [23]. However, the mode of action of homeopathic treatment is controversial. According to one hypothesis, homeopathic drugs act through regulation of gene expression [24]. A different view suggests they act by stimulating an immunological bystander reaction [25,26]. Up to now the effects of homeopathic remedies on the IgE- and mast cell-mediated pathophysiology of allergic rhinitis have not been investigated.

Homeopathic therapies represent an alternative to conventional methods for physicians and patients who seek unconventional treatments. The demand for effective medical alternatives was highlighted by a study in 1990 which estimated that Americans made 425 million visits to providers of unconventional therapy, compared with 388 million visits to all U.S. primary care physicians [27]. In conclusion, the homeopathic nasal spray proved as effective, safe, and well-tolerated a therapy for seasonal allergic rhinitis as the conventional cromolyn sodium nasal spray in this study.

Michael Weiser[a], **Lutz H. Gegenheimer**[b], **Peter Klein**[c]
[a] Institut für Antihomotoxische Medizin und Grundregulationsforschung, Baden-Baden
[b] Reporting and Consulting Services in Clinical Pharmacology, Mannheimx
[c] Datenservice Eva Hoenig GmbH, Rohrbach

Address of corresponding author:
Dr. Michael Weiser
Department of Antihomotoxic Medicine
Dr.-Reckeweg-Str. 2-4, D 76532 Baden-Baden, Germany
Phone: **+49 (0) 7221-501291** Fax: **+49 (0) 7221-501280**

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