Forschende Komplementärmedizin und Klassische Naturheilkunde

Treatment of Inflammatory Diseases of the Upper Respiratory Tract – Comparison of a Homeopathic Combination Preparation with Xylometazoline

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Abstract
Introduction: The primary objective of treatment of inflammatory diseases of the upper respiratory tract (rhinitis, uncomplicated sinusitis) with local decongestants is to relieve obstruction and to improve associated symptoms. Restoration of unrestricted respiration and drainage of the nasal sinuses reduce the risk of further complications (i.e., chronicity). **Objective:** To determine whether the therapeutic effects of the homeopathic combination preparation Euphorbium comp.-Nasal Spray SN are comparable to those of xylometazoline with respect to efficacy and tolerability. **Methods:** Open, multicenter, prospective, active-controlled cohort study in patients with inflammatory processes and diseases of the upper respiratory tract. The primary outcome was to demonstrate non-inferiority of the homeopathic combination preparation to xylometazoline. **Results:** Clinically relevant reductions in the intensities of disease-specific symptoms were observed with both therapies. Non-inferiority of the homeopathic combination preparation to xylometazoline could be shown for all studied variables and in no case did the lower boundary of the 95% confidence interval cross the threshold of 0.5 score points. Tolerability was good for both therapies. **Conclusions:** This cohort study indicates a comparable efficacy and tolerability profile of the homeopathic combination preparation Euphorbium comp.-Nasal Spray SN and the reference substance xylometazoline in patients with inflammatory processes and diseases of the upper respiratory tract.

Introduction

Therapy of inflammatory diseases of the upper respiratory system must focus not only on relieving unpleasant symptoms such as nasal congestion and irritation but also on preventing possible long-term complications in the sinuses, middle ear, and lower respiratory tract.

In viral and bacterial infections and allergic reactions in the nose and throat, swelling of the nasal mucosa and obstruction of nasal respiration develop as a result of arteriolar dilation, edema, and blocked secretion. Frequently associated symptoms that impact the patient's quality of life include impaired sleep, headache, and loss of appetite. On the pathophysiological level, reduced mucociliary clearance increases the risk of both secondary infection (due to impaired nonspecific host defense mechanisms) and blocked secretion [1].

Hence, restoring unimpeded nasal respiration is the first goal of therapy, which often consists of alpha-sympathomimetic decongestant nasal sprays containing oxymetazoline or xylometazoline (Otriven®, Olynth®, etc.). Topical use of these vasoconstrictors improves nasal respiration by decreasing mucosal swelling and reducing mucus secretion [2, 3]. In short-term use, such products are generally well tolerated, but patients who use them for longer periods of time or at higher dosages run the risk of habituation, which is associated with a permanent sensation of nasal obstruction and dryness ("rebound swelling") [4, 5]. Ultimately, secondary damage to the nasal mucosa (rhinitis sicca) may develop under long-term use. Systemic adverse effects are infrequent but insomnia, fatigue, and increases in pulse rate and blood pressure have been known to occur [6].

The combination preparation Euphorbium comp.-Nasal Spray SN (manufactured by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany) is a time-tested modern homeopathic medication frequently used to treat rhinitis

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Ingredient/potency	Indications/symptoms
Euphorbium D4	Inflammation of the respiratory tract (especially of the upper respiratory tract, i.e., rhinitis and sinusitis)
Pulsatilla D2	Inflammation of the respiratory passages and susceptibility to colds; inflammation of the eyes (conjunctivitis); otitis media; measles; headache; neurological disorders; depression
Luffa operculata D2	Rhinitis; hay fever
Mercurius bijodatus D8	Suppurative inflammation of the mucosa of the nose, throat, tonsils, and eyes
Hepar sulfuris D10	Inflammation and suppuration of the mucous membranes; chronic suppuration of the middle ear; peritonsillar abscess; for the treatment of lymphatism; nervous hypersensitivity
Argentum nitricum D10	Migraine

Tab. 1: Composition of Euphorbium comp.-Nasal Spray SN and indications/symptoms of its individual ingredients

and sinusitis. The drug pictures of Euphorbium compositum's six ingredients (Table 1) suggest its use in cases of rhinitis of varying etiology (viral, bacterial, allergic), chronic rhinitis or Rhinitis sicca, and sinus infections and to restore nasal respiration in allergic rhinitis. The therapeutic effects of this homeopathic combination preparation are due to regeneration of damaged tissue, i.e., active healing of pathologies. *In vitro* studies have confirmed the antiviral action of the individual components of Euphorbium comp.-Nasal Spray SN [7].

To directly compare these two therapeutic models and confirm the non-inferiority of the homeopathic medication, an open, multicenter, prospective, active-controlled cohort study was conducted in Germany from 9/2003 to 3/2004. The purpose of the study was to compare the modes of application, efficacy, and tolerability of the two therapeutic regimens through statistical analysis.

Methods

A total of 153 physicians in general medicine and ENT practices were recruited at random (by mail) to participate in the study. Each physician collected (prospective) data on a maximum of five patients. Data on prior illnesses and treatments were obtained from patients' medical files. In keeping with the non-interventional character of post-marketing surveillance studies, data collection was limited to information routinely obtained during everyday practice. Electronic compilation of data took place after completion of treatment ("last patient out"). Data were monitored for completeness and plausibility before statistical evaluation was performed using SAS Version 8.0.

The study was conducted in accordance with German pharmaceutical law (AMG), the Helsinki Declaration, and the German federal guidelines of 12 November 1998 (Federal Gazette #229, 4 December 1998) on planning, implementing, and evaluating post-marketing surveillance studies. According to these guidelines and the AMG, approval by an ethics committee and written patient consent forms are not required for studies of this type. Patient education was left to the discretion of the physicians and conformed to the standards of everyday practice. GCP recommendations were followed to the extent applicable to post-marketing surveillance studies. Participating physicians were not monitored. Copies of the observation and assessment plan were made available to participating physicians [8]. The primary inclusion criterion was a diagnosis of upper respiratory illness (see below). To ensure meaningful conclusions, the following exclusion criteria were applied:

- ongoing therapy for indications covered by the study
- parallel use of other nasal sprays to treat indications covered by the study (non-pharmaceutical adjuvant therapies were permitted).

Treatment was administered in two separate, non-randomized groups. One group (ECN) received Euphorbium comp.-Nasal Spray SN, the other (the XYLO group) received decongestants containing xylometazoline. To avoid/reduce "confounding by indication," each physician reported on only one of the treatment protocols. The physicians were asked to select patients at random, i.e., as they appeared in the practice seeking treatment.

Data were recorded during an initial examination, an optional interim examination, and an exit examination after a maximum of four weeks. The following parameters/criteria were documented; symptom scores were determined by the physician treating each patient.

Patients

- Demographic data, general risk factors, concomitant illnesses
- Rhinitis diagnosed by means of clinical symptoms (preliminary, dry phase: general malaise, burning/tickling in the nose and throat, sneezing; subsequent phases of serous or later usually mucous/purulent secretion)
- Sinusitis diagnosed by means of clinical symptoms including general lassitude, pain in the face and head, (one-sided) obstruction of nasal respiration; rhinoscopy, diaphanoscopy, ultrasound, X-rays as needed

- Duration of illness (scale: < 3 days, 4-7 days, 1-4 weeks, 1-2 months, 3-6 months, 7-12 months, 1-2 years, > 2 years)
- Severity of clinical symptoms (facial pain/headache, sensation of pressure, nasal congestion, rhinitis/nasal secretion, impaired taste/smell, difficulty in breathing, "plugged" ears/earache, sneezing/itchy nose, general lassitude) on a five-point scale (no symptoms, mild, moderate, severe, very severe)

Questions specific to therapy

- Duration and dosage; any changes in dosage during treatment?
- Type and frequency of concomitant therapies used to treat the underlying illness (decongestant nasal sprays not permitted)

Target criteria

- General severity of the inflammation/underlying illness at the beginning/end of the course of therapy (scale: no symptoms, mild, moderate, severe, very severe)
- Change in score of each clinical symptom (see above)
- Timing of first improvement in clinical symptoms during treatment (scale: after first use, 1 day, 2 days, 3 days, 4-7 days, 1-2 weeks, 2-3 weeks, 3-4 weeks, > 4 weeks, no improvement)
- Global assessment of efficacy (scale: very good, good, moderate, ineffective, symptoms worsened)
- Global assessment of tolerability (scale: very good, good, moderate, poor)
- Type and frequency of adverse effects of treatment
- Patient compliance (scale: very good, good, moderate, poor)

Statistics

In an open, active-controlled cohort study of this sort, differences in patients' initial demographic and diagnostic status must be taken into account. Statistical analysis of these differences is performed using ANOVA, the Mantel-Haenszel test, and Fisher's exact test. A propensity score for each patient, calculated through logistic regression, estimates the probability of the patient belonging to a particular treatment group when a specific constellation of background characteristics is present [9, 10]. Propensity scores are then used to stratify patients into structurally homogeneous subclasses, thus ensuring comparability of treatment effects.

The criteria investigated were described in terms of statistical values and absolute and relative frequencies. The two treatment groups were compared for differences in changes in symptom scores between the start and conclusion of therapy. As a working hypothesis, the homeopathic combination preparation was considered non-inferior to the reference medication whenever the left limit of the one-sided 95% confidence interval of the difference between treatment groups was greater than -0.5 (half a score point).

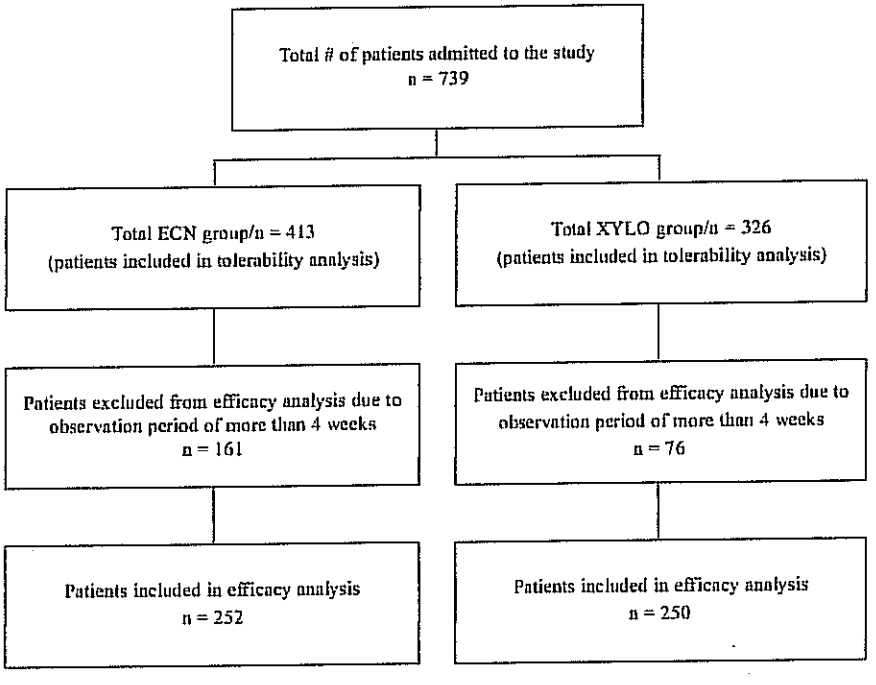

Fig. 1: Flow chart

Results

Patient collective

The participating physicians recorded treatment data on a total of 739 patients (ECN group: n = 413; XYLO group: n = 326). In 237 cases, the exit examination was conducted after more than four weeks. These patients were included in the statistical analysis of tolerability but excluded from the analysis of efficacy, which thus encompassed 252 patients from the ECN group and 250 from the XYLO group (Figure 1).

On average, the membership of the ECN group was younger than that of the reference group (25 vs. 34 years), due primarily to a higher percentage of juvenile participants < 11 years (34% vs. 9%) (Table 2). In both treatment groups, rhinitis (> 70%) and sinusitis (> 30%) were the most commonly diagnosed illnesses (multiple diagnoses were possible). As expected, viral infections were the most frequent cause of illness. Consistent with rhinitis as the most common diagnosis, duration of illness prior to seeking treatment was relatively short in most cases (< 3 days). The physicians rated global severity of the illness as "moderate to severe" in the great majority of cases (84% of patients in both groups).

Treatment

For 98 percent of the ECN group, the prescribed daily dose of the homeopathic nasal spray was one to two sprays per nostril three to five times per day. Xylometazoline was prescribed in concentrations of 0.05-1.0 percent (in the majority of cases, in the form of the products Otriven® and Olynth® at the manufacturers' recommended dosages). The average duration of the observation period was 18.5 ± 6.7 days for the homeopathic combination preparation and comparable in length (16.8 ± 6.1 days) for the reference medication.

Efficacy

To compare the two therapeutic regimens with regard to their therapeutic equivalence, the average change in individual clinical symptoms was determined. Starting from "mild to moderate" or "moderate to severe" symptoms

Parameter	ECN group[a] (252 patients)	XYLO group[a] (250 patients)	p
Demographic data			
Age (in years, average/SD)	25.0/20.8	34.2/20.1	< 0.0001[d]
Gender (n/%)			0.0009[e]
Female	95/37.7	132/52.8	
Male	155/61.5	117/46.8	
Not given	2/0.8	1/0.4	
Type of inflammation (underlying illness) (n/%)[b]			
Rhinitis	192/76.2	180/72.0	0.3088[c]
Sinusitis	91/36.1	99/39.6	0.4618[c]
Rhinitis sicca	28/11.1	7/2.8	0.0003[c]
Hyperplastic rhinitis	22/8.7	10/4.0	0.0430[c]
Atrophic rhinitis	2/0.8	2/0.8	1.0000[c]
Other	35/13.9	22/8.8	0.0909[c]
Cause of inflammation (n/%)[b]			
Viral	166/65.9	146/58.4	0.0662[c]
Bacterial	57/22.6	87/34.8	0.0211[c]
Allergic	27/10.7	20/8.0	0.1920[c]
Other	25/9.9	21/8.4	0.4305[c]
Duration of illness (n/%)[b]			
< 3 days	92/36.5	105/42.0	0.0010[e]
4-7 days	64/25.4	79/31.6	
1-4 weeks	46/18.3	46/18.4	
1-2 months	10/4.0	4/1.6	
3-6 months	12/4.8	7/2.8	
> 6 months	19/7.6	1/0.4	
Not given	9/3.6	8/3.2	
Global severity of inflammation (n/%)			0.0060[e]
Mild	37/14.7	22/8.8	
Moderate	127/50.4	132/52.8	
Severe	85/33.7	78/31.2	
Very severe	1/0.4	9/3.6	
Not given	2/0.8	9/3.6	

[a] patients included in efficacy analysis; [b] multiple diagnoses possible; [c] Fisher's exact test; [d] variance analysis; [e] Mantel-Haenszel test

Tab. 2: Patient demographic and diagnostic data at start of therapy

(nasal congestion, rhinitis/nasal secretion), both groups experienced clinically relevant improvements in all symptoms studied (up to and including complete freedom from symptoms in some cases in each group) by the end of the observation period. After creation of propensity score classes, statistical analysis revealed that for each individual clinical symptom, ECN therapy was comparable in efficacy to xylometazoline therapy (Table 3). In no case did the values for ECN fall outside the 0.5 score point equivalency range. A sensitivity analysis based on unadjusted average differences yielded results not significantly different from the propensity score-adjusted analyses.

An analysis of the change in general severity of the illness from the beginning to the end of therapy yielded comparable results. Average baseline scores declined significantly over the course of the study (from 2.2 to 0.5 for the ECN group and from 2.3 to 0.2 for the XYLO group). With regard to this parameter, too, the two therapies were similarly effective (difference: -0.19 ± 0.55; left limit 95% CI: -0.28).

During the first three days of treatment, as expected, clinical symptoms improved significantly more rapidly in the XYLO group than in the ECN group (Cochran-Mantel-Haenszel test: $p < 0.0001$ for patients included in the efficacy analysis). As the study continued, however, the groups gradually achieved equivalency. The comparable efficacy of the two therapies is also reflected in the overall ratings of therapeutic results (Figure 3). 91% of the patients in the ECN group and 99% in the XYLO group achieved "very good" to "good" results (difference: -0.3 ± 0.6; left limit 95% CI: -0.4). In both groups, patient compliance as an indicator of satisfaction with the assigned treatment was rated "very good" or "good" in more than 94% of cases.

Tolerability

The global assessment of tolerability (which included all patients studied) yielded ratings of "very good" for 87.9% and "good" for 11.9% of the ECN group and 77.3 and 22.1% respectively for the XYLO group, indicating a significant difference between treatment groups in favor of ECN (Mantel-Haenszel test: $p < 0.0001$).

In the XYLO group, three cases of undesired effects were attributed to the medication (symptoms: burning, dryness, and local irritation of the nasal mucosa; elevated blood pressure). No adverse effects were reported in the ECN group.

Discussion

Whether viral (rhinovirus, adenovirus, echovirus), bacterial (Streptococcus pneumoniae, Haemophilus influenzae, streptococci, staphylococci), or allergic (e.g., grass pollen) in origin, inflammation of the upper respiratory passages is often associated with swelling of the nasal mucosa. Local decongestants, in addition to other medications, are generally indicated to relieve cardinal symptoms such as obstructed nasal respiration, nasal mucus secretion, and impaired sleep. In addition to relieving these subjective symptoms, therapy must also focus on preventing secondary infections in the sinuses and lower respiratory tract. Symptomatic treatment of rhinitis/sinusitis is also of economic importance, in that it reduces absenteeism at work and school. For example, in the USA in 1997, upper respiratory infections ("common colds") caused 26 million missed school days, 23 million missed work days, 27 million doctor's visits, and costs of around 2 billion US dollars [11].

As homeopathic treatment is a very individual form of therapy, differences in the distribution of baseline criteria between the groups investigated in this study may exist, making it difficult to ensure comparability of the two groups. Rosenbaum and Rubin [9] and D'Agostino [10] developed the propensity score method of reducing or compensating for baseline differences between groups in non-randomized studies. Estimated values describing actual effects thus become more meaningful and robust. Although more recent studies by Lüdkte et al. [12] and Weber et al. [13] suggest that this method can produce heterogeneous results, especially when the treatment groups differ significantly with regard to diagnoses and severity of the illnesses, this method is frequently used and for the most part positively rated. What does this mean for the current study? Its comparative estimates cannot be considered definitive but are nonetheless meaningful and certainly constitute a suitable basis for formulating a hypothesis, especially since several different methods of analysis produced similar results.

Whether the results of studies conducted under the circumstances of everyday practice are as valid as those of controlled clinical studies is a controversial issue that has generated much discussion. A meta-analysis conducted by Benson and Hartz [14] found a great deal of agreement in the results of clinical and post-markting surveillance studies, but its results were only partially confirmed by a more recent study by Deeks et al. [15].

Given the limited scientific reliability of post-marketing surveillance studies, the findings of the current study leave plenty of room for medical and methodological discussion [16]. Nonetheless, post-marketing surveillance studies are of inestimable value in assessing therapeutic models that are difficult to explore in randomized studies. Furthermore, they are more suited to investigate daily medical practice in patient populations not subject to the restrictions of randomized studies. It is worth mentioning that narrowly defined inclusion and exclusion criteria may eliminate anywhere from 9 to 51 percent of patients as potential study participants [19].

The current prospective, active-controlled cohort study compared the efficacy and tolerability of two medications used for the listed indications. Patients were treated with either the alpha-sympathomimetic drug xylometazoline or the homeopathic combination preparation Euphorbium

Target criteria (clinical symptoms)	ECN group[a] Baseline (A/SD)[c]	Final[b] (A/SD)	XYLO group[a] Baseline (A/SD)	Final (A/SD)	A/SD difference between therapies
Facial pain/headache	1.3/1.1	0.1/0.4	1.7/1.0	0.1/0.3	-0.05/0.39
Sensation of pressure	1.5/1.1	0.2/0.5	1.8/1.0	0.1/0.4	-0.07/0.42
Nasal congestion	2.3/0.8	0.4/0.7	2.4/0.9	0.2/0.4	-0.21/0.55
Rhinitis/nasal secretion	2.1/0.9	0.4/0.6	2.2/0.9	0.3/0.5	-0.16/0.55
Impaired taste/smell	1.2/1.0	0.2/0.5	1.5/1.1	0.1/0.4	-0.02/0.40
Difficulty in breathing	1.1/1.0	0.1/0.4	1.0/1.0	0.1/0.3	-0.04/0.33
Plugged ears/earache	0.8/1.0	0.1/0.3	1.0/1.0	0.1/0.3	+0.01/0.27
Sneezing/itchy nose	0.9/1.0	0.1/0.4	1.1/1.0	0.0/0.2	-0.10/0.32
General lassitude	1.5/1.1	0.1/0.4	1.8/1.0	0.1/0.4	-0.05/0.39

[a] patients included in efficacy analysis; [b] Final = exit examination; [c] A = arithmetical average; SD = standard deviation

Tab. 3: Differences in reduction in symptoms studied (scale: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). Positive differences indicate greater reduction with Euphorbium comp.-Nasal Spray SN; negative differences indicate greater reduction with xylometazoline.

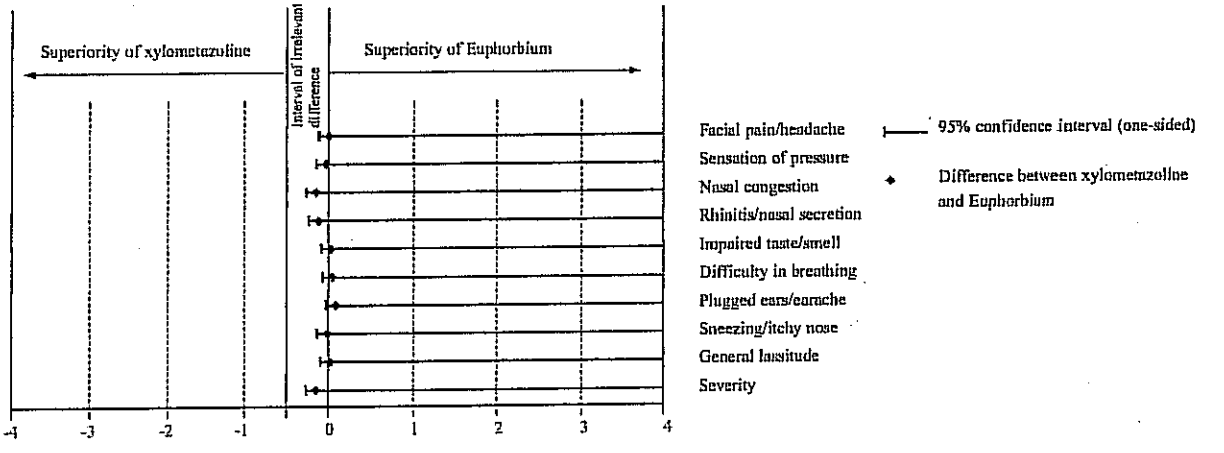

Fig. 2: Difference in reduction in symptoms studied between the therapeutic alternatives Euphorbium comp.-Nasal Spray SN and xylometazoline (differences with one-sided confidence intervals adjusted according to propensity scores and initial values; patients included in efficacy analysis).

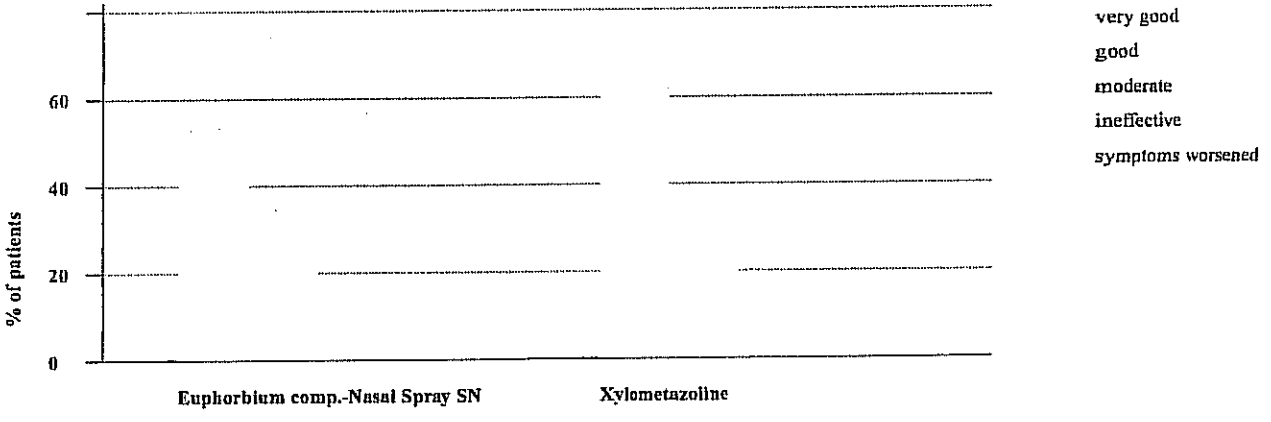

Fig. 3: Global rating of therapeutic results achieved (ECN group: n = 252; XYLO group: n = 250; patients included in efficacy analysis).

comp.-Nasal Spray SN. With 739 patients, the study encompassed a sufficiently large number of cases to produce reliable statements about the efficacy and tolerability of both of these topical therapies.

The above-mentioned diagnostic criteria (including clinical symptoms and – as needed – rhinoscopy, diaphanoscopy, and ultrasound) were geared to routine procedures in established medical practices. The target parameters used to assess efficacy were also geared to routine medical practice and can be considered clinically relevant to the field of application under investigation, namely, inflammation of the upper respiratory tract.

The predominant indication was rhinitis, with patients experiencing "moderate to severe" symptoms when the study began. Changes in the severity of disease-specific individual symptoms over the course of treatment were investigated. Initially, the symptoms "nasal congestion" and "rhinitis/nasal secretion" were most pronounced. The data indicate that the intensity of all specific symptoms declined significantly during the course of treatment; the average patient was almost symptom-free upon conclusion of therapy. Statistical comparison of the two groups indicates that the two therapies were therapeutically equivalent with regard to all symptoms investigated. In other words, treatment with the homeopathic combination preparation Euphorbium comp.-Nasal Spray SN was as effective as treatment with the alpha-sympathomimetic drug xylometazoline.

The maximum period of observation (four weeks) was deliberately set high to include cases of acute as well as chronic illness (e.g., chronic sinusitis). The average observation period was 18.5 ± 6.7 days for the homeopathic combination but significantly shorter (16.8 ± 6.1 days) for the reference medication. The question arises, did the study document effects of treatment or effects of the passage of time? But in spite of this relatively wide window, the authors believe that the study design was appropriate for discovering the effects of these therapies and that the majority of improvements recorded were not the result of spontaneous remission. In this context, it is important to note that several clinical studies have proven the efficacy of xylometazoline, the drug selected as the reference substance, and found that its effects were statistically significant and therefore clinically relevant [2-5]. As early as the interim examination (after 12.4 ± 4.5 days for the ECN group and 12.2 ± 4.1 days for the XYLO group), propensity-score adjusted values indicate non-inferiority of the test medication with regard to most of the target criteria (exceptions were nasal congestion and severity of the illness; 95% CI -0.63 in each case). Ultimately, resolving the question of spontaneous remission would require a three-armed study incorporating placebo.

In the majority of cases, global tolerability of both therapies was rated positively after the average treatment period (18.5 days for the ECN group and 16.8 days for the XYLO group). From the perspective of long-term use, it is of interest that Euphorbium comp.-Nasal Spray SN received a higher percentage of "very good" and "good" ratings and that a statistically significant difference between the treatment groups was confirmed in favor of the homeopathic combination preparation. Although the data from this study indicate that the efficacy profiles of the two therapies are essentially comparable, the underlying therapeutic models are different. As a vasoconstrictor, xylometazoline produces temporary symptomatic relief. In contrast, the efficacy of Euphorbium comp.-Nasal Spray SN is based on healing of the disease process. Recent studies indicate that individual components of this homeopathic combination have broad antiviral and immunomodulatory effects [7, 20-22]. In addition to effectively reducing subjective symptoms, as proven by the current study, these ingredients also tackle the cause of the illness with no risk of rebound congestion (rhinitis medicamentosa) or habituation.

Expression of thanks

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