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Prospective Cohort Trial of *Euphrasia* Single-Dose Eye Drops in Conjunctivitis

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ABSTRACT

Introduction: Eye drops made from *Euphrasia rostkoviana* Hayne have been used in anthroposophical medicine for more than 70 years for the structuring of the fluid organism in the eye, especially in inflammatory and catarrhal conjunctivitis. The aim of this prospective cohort trial was to describe the efficacy and tolerability of these eye drops in a community-based setting. To evaluate these questions, prospective cohort studies are the best method. This enables the investigator to attain real insights as to which treatment administered related to specific results in a specific group of patients.

Design: Prospective, open label, one-armed, multicentered, multinational cohort trial.

Setting: The trial was carried out in the clinics of 12 experienced anthroposophical general practitioners and ophthalmologists in Germany and Switzerland.

Patients: Patients with inflammatory or catarrhal conjunctivitis, treated with *Euphrasia* single-dose eye drops were included in the trial.

Intervention: One drop of *Euphrasia* single-dose eye drops 1–5 times a day was prescribed. The prescription was determined solely by medical therapeutic needs.

Outcome Measures: Efficacy variables were: redness, swelling, secretion, burning of the conjunctiva, and foreign body sensation. Tolerability variables were: conjunctival reddening, burning of the conjunctiva, foreign body sensation, and veiled vision. All symptoms were given for the right or left eye separately, with degree of severity in relation to baseline after approximately 7 days (±3 days; first follow-up examination) and after approximately 14 days (±3 days; second follow-up examination). If, after the first follow-up, all symptoms had disappeared, no second follow-up was done.

Results: Sixty-five (65) patients fulfilled the inclusion criteria for the protocol evaluation. A complete recovery was seen in 53 patients (81.5%) and a clear improvement in 11 patients (17.0%). A slight worsening could only be determined in 1 patient in the second week of treatment (1.5%). No serious adverse events were observed during the entire trial. The efficacy and tolerability were evaluated by the patients and doctors as "good" to "very good" in more than 85%.

Conclusion: *Euphrasia* single-dose eye drops can effectively and safely be used for various conjunctival conditions by general practitioners and ophthalmologists. A dosage of one drop three times a day seems to be the general prescribed dosage.

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INTRODUCTION

Clinical trials are conducted to evaluate safety and efficacy of drugs, medical devices, and other treatments. Depending on the question that is being evaluated, different trial methods are available. With double-blind placebo-controlled trials it is possible to evaluate the benefit of a drug without the interfering parameters such as the healing intention of the doctor or the expectations from the patient's side. Usually the trial is done in a small, well-defined patient group (Freedman, 1987). With a prospective cohort trial it is possible to evaluate a therapy under everyday conditions including different age groups and the intentions and expectations of patients and doctors (Hornung, 1989).

There are several shortcomings of a double-blind placebo-controlled trial. First, not more than 2%–3% of the population with the indication of interest are evaluated (Gotay, 1991). The selection is done in such a way that the investigated population is, in general, totally different from the population in the clinic of a general practitioner (Feinstein, 1983). Second, the healing intention of the doctor, which is generally a benefit, is omitted and can now also be viewed as a drawback because this is an essential aspect of complementary therapy. Last, as a result of being placed into a random placebo grouping, the patient is unable to select a form of therapy that he prefers (Horwitz, 1987).

On the other hand, the essential drawbacks of prospective cohort trials are a loss of objectivity due to data protection reasons and the lack of a randomized control group.

In Europe, and especially in Germany, complementary therapy is widely used. As a result of this long-lasting tradition and the awareness of the drawbacks of double-blind placebo-controlled trials, the German medical law *(Arzneimittelgesetz)* expressly refers to trial concepts such as the prospective cohort trial for the evaluation of complementary medicines.

In the following, the results of a prospective cohort trial for *Euphrasia* single-dose eye drops against conjunctival inflammation is presented.

Inflammation in the conjunctiva is the most frequent illness in the eye and is caused by exogenous factors such as viruses, bacteria, rickettsia, fungi, dust, irritants or toxic substances, and endogenous factors. In central Europe conjunctivitis appears in approximately 13.5 per 1,000 people (Sheldrick et al., 1992) with the most frequent reasons being allergic and toxic conjunctivitis. Viral infections are also one of the most common causes for acute conjunctivitis (Jackson, 1993). Bacterially caused conjunctivitis is, on the other hand, relatively rare (Hansen, 1997). In older people conjunctivitis caused by irritants due to deficient moisture plays an important role. This is also exacerbated by long-term wearing of contact lenses (Friedlaender, 1996; Suchecki et al., 1996), or the wrong and continuous use of eye drops with preservatives (Soparkar et al., 1997). Mostly it is only a limited, mild illness, although severe forms also do exist. Endocrine ophthalmopathy and Sjögren's syndrome, among others, belong to the systemic illnesses that are related to conjunctivitis (Hansen, 1997).

In exogenous conjunctivitis the harmful agent leads to an edema in the epithelium, cell death, and the dissolving of the epithelium. This leads to an epithelial hypertrophy, or the formation of granuloma, or chemosis and the formation of follicles (Hansen, 1997). The essential symptoms of conjunctivitis are hyperemia due to a conjunctival injection, chemosis, watery eyes, watery, slimy or purulent excretion with stickiness, swollen lids and pseudoptosis, lymph-follicle hypertrophy, and membranes or pseudo-membranes. Normally, conjunctivitis does not impair vision (Judge, 1992; Mader and Stulting, 1992; Bertolini and Pelucio, 1995; Friedlaender, 1993). Subjectively the patient experiences a foreign body sensation as well as burning and pressure around the whole eye. The increased secretion leads to stickiness of the lids in the morning, which is experienced as unpleasant (Friedlaender, 1995).

The therapy is essentially directed by etiology, the degree of severity, and the course of the illness. Conjunctivitis can easily be treated if diagnosed and treated in time. More serious damage can, however, occur with insufficient diagnosis and therapy (Jackson, 1993). Broad-spectrum antibiotics (Snyder and Glasser, 1994), artificial tears without preservatives, antihistamines (Montan et al., 1994; Struck et al., 1998), and also nonsteroidal anti-inflammato-

ries (Tauber et al., 1998), as well as pain killers, or vasoconstrictory medications are often used as therapy. Corticosteroids and topical antibacterials should only be used with care because they can lead to complications or disguise the actual cause of the illness (Weber and Eichenbaum, 1997).

Medications made from *Euphrasia officinalis* L. have been used since the 16th century in ophthalmology (Hahn, 1995). The plant contains iridoglycosides (Aucubin), euphroside, tanning agents, bitter substances and some etheric oils (Thesen et al., 1993). Until now, no substantiated toxicity has been described for lower concentrations of the plant or extracts from it (Trovato et al., 1996). An immunomodulating effect is assumed for *Euphrasia* (Wagner, 1996). In anthroposophical medicine, *Euphrasia* single-dose eye drops are used for the structuring of the liquid organism in the eye region or in catarrhal conjunctivitis. Medication made from *Euphrasia* is also successfully used in homeopathy for conjunctivitis (Central Council for Research in Homeopathy, 1989).

The aim of this prospective cohort trial was to describe the efficacy and tolerability of *Euphrasia* single-dose eye drops in inflammatory and catarrhal reactions in the conjunctiva, caused, for example, by irritants such as overexertion of the eyes, wind, dust, or pollen in a community-based setting.

MATERIALS AND METHODS

All patients with inflammatory or catarrhal conjunctivitis, treated with *Euphrasia* single-dose eye drops were included into the trial. They were treated at the clinics of 12 experienced anthroposophical general practitioners and ophthalmologists in Germany and Switzerland. Because of the trial concept, only patients for whom the physician had already prescribed *Euphrasia* single-dose eye drops could be enrolled into the trial.

One-hundred grams of *Euphrasia* single-dose eye drops (WALA Heilmittel GmbH, Eckwälden/Bad Boll, Deutschland) contain *Euphrasia* e planta tota ferm 33c D2 10 g; Rosa aetherolum D7 (etheric oil of the roses) aquos. (Homöopathisches Arzneibuch [HAB], SV.5b) 10 g; according to GHP, method 40b, 16.3 and 15- communally potentised in two levels and sodium chloride and bicarbonate, which serves as isotonic medium.

The recommended dose of *Euphrasia* single-dose eye drops is one drop, 1–3 (up to 5) times a day in the conjunctival sac, which is normally sufficient. In acute situations, more frequent application may be necessary. The prescription was determined purely by the medical-therapeutic need.

In the baseline investigation the diagnosis was made and demographic as well as anamnestic data were obtained. Pretreatment was established, the *Euphrasia* single-dose eye drop dosage was determined, and other medication noted.

As efficacy parameters the variables "reddening," "swelling," "secretion," "burning of the conjunctiva," and "foreign body sensation" were investigated. The variable reddening was subdivided into conjunctival, ciliary, and mixed injection; swelling into chemosis and follicle swelling; secretion into serous and thick discharges. All parameters were investigated for the right and left eyes separately; the degree of severity (not available, mild, medium, severe) in relation to baseline, after approximately 7 ($\pm$3) days (first follow-up examination) and after 14 ($\pm$3) days (second follow-up examination).

For the tolerability investigation conjunctival reddening, burning of the conjunctiva, foreign body sensation, veiled vision, and undesired effects because of the medication were obtained and documented.

Conjunctival reddening, burning, and foreign body sensation were noted, as described for the efficacy evaluation. The duration of veiled vision was divided into the categories: not available; short $<$10 seconds; medium, 10–30 seconds; and long, $>$30 seconds.

The doctor as well as the patient evaluated and rated the effectiveness and tolerability of the therapy as very good, good, satisfactory, or poor.

The evaluation of the data was purely descriptive. All effectiveness and safety parameters were represented in frequency tables. The statistical calculation was done with the soft-

TABLE 1. AGE DIVISION OF PATIENTS IN YEARS

	n	*Mean value*	*Standard deviation*	*95% confidence interval*		*Minimum*	*Maximum*
Men	27	33.1	25.3	23.1	43.1	1.3	82.0
Women	38	37.1	27.4	28.1	46.1	0.5	84.0
Total	65	35.4	26.4	28.9	42.0	0.5	84.0

The division of age between men and women is comparable in both groups. Patients between the ages of 6 months and 84 years were taken up in the trial.

ware package SAS® System for Windows, Release 6.12 (SAS Institute Inc., Cary, NC).

RESULTS

Eighty (80) patients were enrolled into the prospective cohort trial. The data of 15 patients were excluded from the main evaluation. The data of 1 patient were not included because it was clearly evident from the remarks on the questionnaire that the medication could not have been applied. In 14 patients the time period between baseline examination and last follow-up examination was more than 17 days (14 + 3). After evaluation of the data, the administering doctors were asked via telephone for an explanation of the latest follow-up visit. The following reasons were given:

1. In 8 patients, organizational reasons were given. They could not get to the practice earlier because they were too old, had to drive too far, or it was too difficult for other reasons. In all these patients the conjunctivitis had cleared up after, at the most, 14 (±3) days, according to the doctors.
2. In 4 patients the reason was a recurring illness (twice hayfever, one recurring, feverish infection, one house dust allergy). Because the irritant causing the conjunctivitis could not be avoided, the *Euphrasia* single-dose eye drops could not heal the conjunctivitis.
3. In 2 patients the conjunctivitis was caused by sicca syndrome, which could not be influenced by the *Euphrasia* single-dose eye drops.

These patients were not included into the main evaluation because they were not treated according to the trial plan. Therefore, the data of 65 patients were evaluated. Of these, 27 were male (41.5%) and 38 female (58.5%). The average age of the patients was 35.4 years (men 33.1, women 37.1). The men and women are comparable with regard to age (Table 1).

The reason for the conjunctivitis as outlined by the patients can be divided as follows. Irritation was mentioned by 13 patients (20.0%) whereas a combination of irritation and wind/dust was mentioned by 7 patients (10.8%); wind/dust and pollen was given as a reason by 12 patients (18%); 3 patients (4.6%) gave a combination of irritant or wind/dust

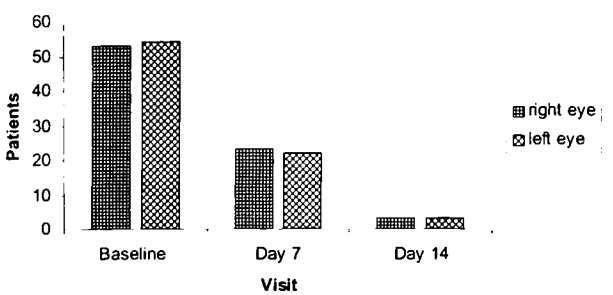

FIG. 1. Course of conjunctival reddening. At baseline the right eye is affected in 53 patients, the left in 54 patients. At the first follow-up examination after 7 (±3) days, only 23 right and 22 left eyes are still affected. At the second follow-up after 14 (±3) days this symptom is only found in 3 eyes on each side.

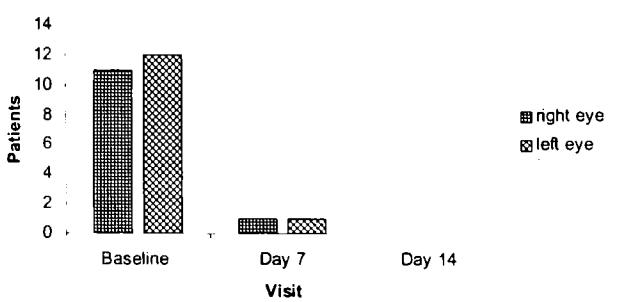

FIG. 2. Course of ciliary reddening. At baseline, the right eye is affected in 11 patients, the left in 12 patients. At the first follow-up after 7 (±3) days, only 1 eye on each side is still affected. At the second follow-up after 14 (±3) days, no patients present with this symptom.

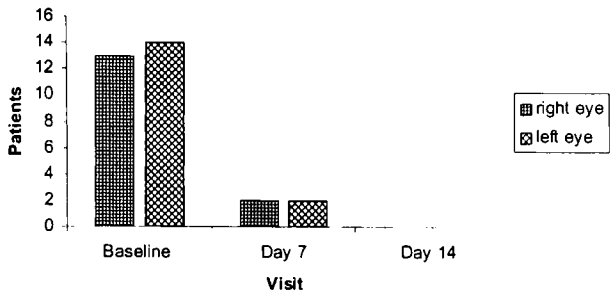

FIG. 3. Course of mixed injection. At baseline, the right eye is affected in 13 patients, the left in 14 patients. At the first follow-up after 7 (±3) days, only 2 eyes on each side are still affected. At the second follow-up after 14 (±3) days, no patients present with this symptom.

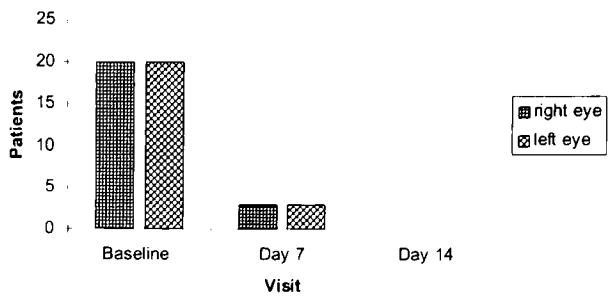

FIG. 5. Course of follicle swelling. At baseline, both eyes in 20 cases each are affected. At the first follow-up after 7 (±3) days, only 3 eyes on each side are still affected. At the second follow-up after 14 (±3) days, no patients present with this symptom.

and other factors; 17 patients (26%) named other not further described reasons as a trigger and 13 patients (20%) gave no reason. Thirteen (13) of the 65 (30%) patients also mentioned an allergy as reason; 2 patients wore contact lenses.

Of the 65 patients, 53 (81%) had conjunctivitis in both eyes, and 6 (9% each) conjunctivitis in the left or right eye. Ten patients (15%) (4 men and 6 women) had used a pretreatment consisting of various allopathic or complementary medical preparations. Three patients (4.5%) mentioned chronic recurring conjunctivitis in their history. Otitis media, acute bronchitis, pollen allergy, rhinitis, chronic rhinopharyngitis, sinusitis, allergic rhinitis, bronchial asthma, and various allergies were described in the histories as general illness, which could have been the cause of conjunctivitis.

The average treatment period was 11 days. The difference between maximum and minimum was 14 days (17 or 3 days).

One patient (1.5%) only appeared at baseline, 29 patients (44%) ended the prospective cohort trial with the follow-up on day 7 (±3) and 35 patients (53%) on day 14 (±3).

At the beginning of the prospective cohort trial, conjunctival reddening appeared in 53 right eyes and 54 left eyes, which had cleared up completely after 6 to 14 (±3) days (Fig. 1). Ciliary reddening was determined at baseline in 11 right eyes and 12 left eyes and cleared up completely after, at the most, 14 (±3) days (Fig. 2). Mixed injection was determined at baseline in 12 right eyes and 14 left eyes and had also cleared up after, at the most, 14 (±3) days (Fig. 3). In 45 right eyes and 46 left eyes in which a burning conjunctiva had been diagnosed, all except 1 eye had healed after 14 (±3) days (Fig. 4). Of the 20 right and left eyes each in which follicle swelling had been diagnosed, all were healed after 14 (±3) days (Fig. 5). The same in the 13 right eyes and 12 left eyes in which a thick discharge had been diagnosed (Fig. 6).

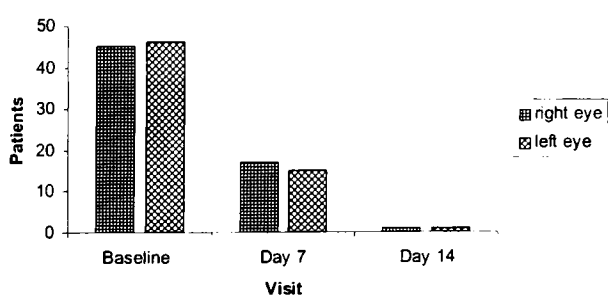

FIG. 4. Course of burning of conjunctiva. At baseline, the right eye is affected in 45 patients, the left eye in 46 patients. At the first follow-up after 7 (±3) days, only 17 right and 15 left eyes are still affected. At the second follow-up after 14 (±3) days, this symptom is only determined in 1 eye on each side.

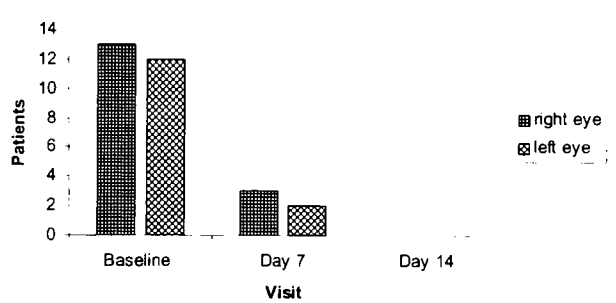

FIG. 6. Course of thick discharge. At baseline, the right eye is affected in 13 patients, the left eye in 12. At the first follow-up after 7 (±3) days, only 2 right and 3 left eyes are still affected. At the second follow-up after 14 (±3) days, no patients present with this symptom.

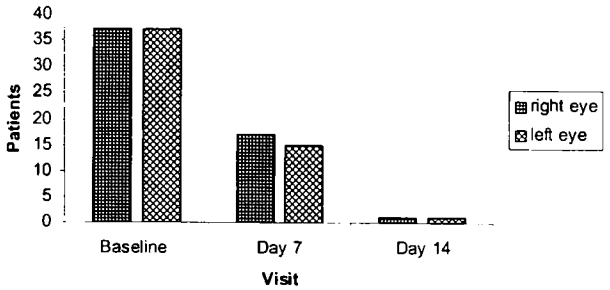

FIG. 7. Course of serous secretion. At baseline, both eyes are affected in 37 patients. At the first follow-up after 7 (±3) days, only 17 right and 15 left eyes are still affected. At the second follow-up after 14 (±3) days, this symptom is only found in 1 eye on each side.

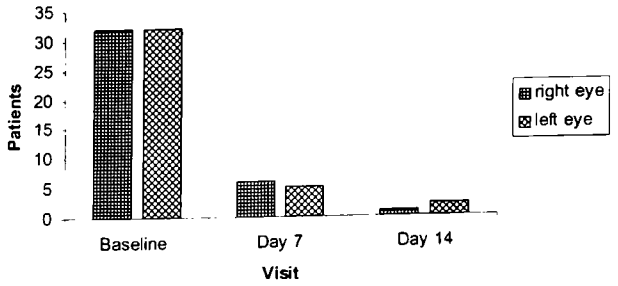

FIG. 8. Course of foreign body sensation. At baseline, both eyes are affected in 32 patients. At the first follow-up after 7 (±3) days, only 6 right and 5 left eyes are still affected. At the second follow-up after 14 (±3) days, this symptom is only determined in 1 right and 2 left eyes.

Also, of the 37 right or left eyes with a serous secretion, all were healed after 14 (±3) days (Fig. 7). A similar result was observed in the 32 right or left eyes with a foreign body sensation, except for 1 right and 2 left eyes (Fig. 8), and the 20 right and 24 left eyes afflicted with swelling (chemosis) (Fig. 9).

In 53 patients (81%) there was complete recovery; in 22 patients at the follow-up on day 7 (±3) and in 31 at follow up on day 14 (±3). Eleven (11) patients showed a distinct improvement of symptoms; in only 1 case was there a slight worsening of conjunctival reddening, serous secretion, and in the burning of the conjunctiva. These did not appear at the first follow-up, but appeared at the second follow-up with severity 1 (mild).

As a whole, the character and frequency of the symptoms decreases as can be seen clearly in Figure 1 to Figure 9. At the first follow-up there are no longer any severe symptoms. In the second follow-up there are also no longer any symptoms of medium severity.

The tolerability of the medication was very good. Only three patients reported mild to moderate symptoms after 7 days, and only one after 14 days (Table 2). It can be assumed that this corresponds to the normal course of the illness and not a side effect of the medication. A correlation to the medication is unlikely according to the World Health Organization (WHO) criteria.

No undesirable serious adverse event occurred due to the medication during the entire prospective cohort trial.

On average the medication was prescribed and used three times a day. In total there was deviation from the prescribed therapy in only four cases; three patients needed less and one patient needed more than the doctor had prescribed.

The effectiveness evaluation of the preparation by the patients indicated that 56 patients (88%) evaluated the medication as good to very good, 6 patients (9%) as satisfactory, and 1 patient as poor. Two patients did not give an evaluation. The doctors evaluated the therapy similarly. In 57 patients (88%) it was evaluated as good to very good, in 5 patients (7.5%) as satisfactory and in 2 patients as poor. No evaluation was given for 1 patient. The tolerability of the preparation was similarly evaluated by the patients and the doctors. Sixty-one (61) patients (94%) described the tolerability as good to very good and 2 patients (3%) as satisfactory. Two patients did not give an evaluation. The doctors evaluated tolerability as good to very good for 63 patients (97%). It was not evaluated satisfactory or poor by any doctor. No evaluation was given for 2 patients (Table 3).

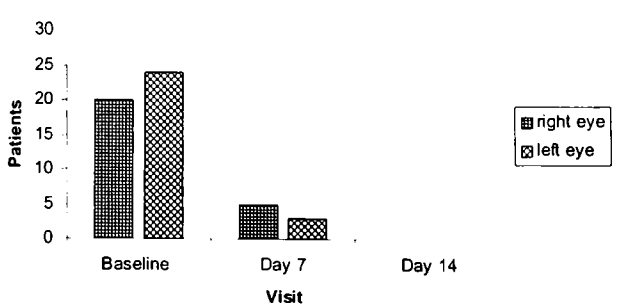

FIG. 9. Course of swelling (chemosis). At baseline, the right eye is affected in 20 patients, the left eye in 24. At the first follow-up after 7 (±3) days, only 5 right and 3 left eyes are still affected. At the second follow-up after 14 (±3) days, no patients present with this symptom.

TABLE 2. TOLERABILITY FOR PATIENTS WITH SYMPTOMS

Patient no.	*Right eye*			*Left eye*			*Right eye*			*Left eye*		
	Day 7						*Day 14*					
	Reddening[a]	*Burning*[a]	*Veiling*[b]	*Reddening*	*Burning*	*Veiling*	*Reddening*	*Burning*	*Veiling*	*Reddening*	*Burning*	*Veiling*
50	1	0	0	1	0	0	–	–	–	–	–	–
59	1	1	0	1	1	0	–	–	–	–	–	–
78	2	0	0	2	0	0	1	0	0	1	0	0

[a]0: not available, 1: mild, 2: medium; [b]0: not available, 1: short (<10 sec.)

In all three patients there is a regression of the efficacy parameters in relation to baseline. It can be assumed that this concerns the natural course of the illness and is not a side effect of the medication.

TABLE 3. EVALUATION OF EFFICACY AND TOLERABILITY OF THE THERAPY BY PATIENT AND DOCTOR

	Evaluation of efficacy				*Evaluation of tolerability*			
	Patient		*Doctor*		*Patient*		*Doctor*	
Evaluation	*Number*	%	*Number*	%	*Number*	%	*Number*	%
Very good	40	61.5	46	70.8	51	78.5	54	83.1
Good	16	24.6	11	16.9	10	15.4	9	13.8
Satisfactory	6	9.2	5	7.7	2	3.1	0	0
Poor	1	1.5	2	3.1	0	0	0	0
Missing	2	3.1	1	1.5	2	3.1	1	3.1

A maximum of two values were not captured.
In 55 cases (85%) the evaluation of efficacy with good or very good corresponds with patients and doctors. With the evaluation of tolerability, even in 60 cases (92.3%).

In only one patient was the effectiveness evaluated as poor by the doctor as well as the patient. This patient had mild symptoms at all examinations in the form of conjunctival reddening, burning of the conjunctiva, and foreign body sensation. He adhered to the examination times and administered, as prescribed, five times a day.

DISCUSSION

Euphrasia single-dose eye drops are used in anthroposophical medicine for the restructuring of the fluid organism of the eye, e.g., in catarrhal conjunctivitis. In addition to the good efficacy reported by the doctors and the patients, a significant advantage of this medication is the fact that it contains no preservatives and can therefore also be used effectively over a long period of time.

The aim of this prospective cohort trial was to show the efficacy and tolerability of *Euphrasia* single-dose eye drops at the recommended dosage of one drop 1–5 times daily in the conjunctival sac in patients with inflammatory and catarrhal reaction in the conjunctiva, which was caused by irritations such as overexertion of the eyes, wind, dust, or pollen. Sixty-five (65) patients from age 6 months to 84 years were examined for this in 12 doctor's practices. Prescriptions were determined purely by medical therapeutic need.

The symptoms of conjunctivitis were documented for the right and the left eye in the four degrees of severity not available, mild, medium, and severe in relation to baseline after 7 (±3) and 14 (±3) days. Tolerability was examined after 7 (±3) and 14 (±3) days. The doctor as well as the patient gave an evaluation of the efficacy and tolerability of the therapy at the end of the treatment.

A prospective cohort trial is suited to substantiating a known efficacy and to provide a closer description of tolerability. It is also a very good study instrument for investigating therapies in a practice situation (Höning et al., 1998). For the statistical evaluation only descriptive events are used. The age division was typical for conjunctivitis (Masi et al., 1993; Friedlaender, 1995), and there was no gender preference.

The prospective cohort trial was carried out without monitoring. In 14 patients a time period of more than 14 (±3) days was determined in the examinations. A plausibility test of the captured data led in these patients to a telephone call to the treating doctors. The reasons for a supposed bad response to the therapy was therefore cleared (8 times organizational reasons, 4 times other recurring infections, 2 times sicca syndrome). Because these patients underwent their follow up examination significantly later than planned, they were not taken up in the total evaluation.

A distinct improvement of conjunctivitis after 7 (±3) and 14 (±3) days, or the healing of follicle swelling, thick discharge, ciliary reddening or mixed injection, can be related to the therapy.

In a double-blind, placebo-controlled study of *Euphrasia* eye drops in 44 patients, a complete healing of the verum group could be shown (Central Council for Research in Homeopathy, 1989). This supports the good effec-

tiveness of the WALA *Euphrasia* single-dose eye drops in the results as presented here.

Considering the length of treatment and the fact that there were no undesired effects due to the medication, as well as the fact that a slight worsening of the symptoms could only be observed in one patient, it can be asserted that *Euphrasia* single-dose eye drops are a very effective medication. The good correspondence between the subjective evaluation by the doctors and patients, and the objectively gained data speaks for the efficacy and tolerability of the medication. The high degree of compliance is also a sign that the patients found the therapy to be effective and helpful.

CONCLUSION

Euphrasia single-dose eye drops can be used effectively for allergic conjunctivitis, conjunctivitis due to the external irritants of wind and pollen, or other reasons not further described. It leads to a complete disappearance of symptoms within 3 to 17 days in more than 95% of patients. These results relate to the double-blind, placebo-controlled study with homeopathic *Euphrasia* eye drops as described in the literature. A dosage of three times daily proved to be optimal in the majority of patients. There were no side effects. A mild irritation of the eyes was described in 1 of the 65 cases. Effectiveness was described by patients and doctors as good to very good in approximately 88% of the cases. This was true for tolerability even in 94% to 97% of the cases. As a whole this is an effective therapy. In addition to the good effectiveness and tolerability, a significant advantage of the medication used in this trial is the fact that it does not contain any preservatives and is therefore also well suited for long-term use.

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DECLARATION OF INTEREST

Dr. Stoss commenced the study when working for an independent research organization but has since joined the pharmaceutical company Pharma Natura, a company with an agency agreement with WALA. This author has no financial stake in the product reported.

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