Clinical and Experimental Allergy, 1997, Volume 27, pages 552–558

Fluticasone propionate nasal spray is more effective and has a faster onset of action than placebo in treatment of rhinitis medicamentosa

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Summary

Background Controversy still exists about the treatment of rhinitis medicamentosa and treatment has never been objectively evaluated.
Objective To study the effect of fluticasone propionate aqueous nasal spray compared to placebo nasal spray in the treatment of rhinitis medicamentosa.
Methods A parallel randomized, double-blind study was conducted to evaluate the treatment of rhinitis medicamentosa. Two groups containing 10 patients with rhinitis medicamentosa in each group stopped their overuse of nasal vasoconstrictor spray immediately and were treated with either fluticasone propionate nasal spray once daily 200 μg, or placebo nasal spray for 14 days. The nasal mucosal swelling was recorded with rhinostereometry, acoustic rhinometry and a peak inspiratory flow meter. Nasal stuffiness was estimated on a visual analogue scale in the morning and in the evening of each day.
Results The mucosal swelling decreased after 7 and 14 days of treatment with fluticasone propionate as well as placebo, but the reduction was significantly greater after treatment with fluticasone propionate. The symptom scores for nasal stuffiness showed a marked reduction during the treatment period in both groups, but there was a faster onset of symptom reduction after treatment with fluticasone propionate.
Conclusion Fluticasone propionate is more effective and has a faster onset of action than placebo in the treatment of rhinitis medicamentosa. An adequate treatment of these patients consists of a combination of vasoconstrictor withdrawal and a topical corticosteroid to alleviate the withdrawal process.

Keywords: acoustic rhinometry, fluticasone propionate, rhinitis medicamentosa, rhinostereometry, PNIF

Clinical and Experimental Allergy, Vol. 27, pp. 552–558. Submitted 14 July 1996; revised 26 September 1996; accepted 16 October 1996.

Introduction

Rhinitis medicamentosa is caused by nosedrop overuse and is characterized by nasal obstruction and a loss of responsiveness to nasal decongestants. The pathophysiology of rhinitis medicamentosa is still unknown. It is very difficult to study the pathophysiology since there are many reasons why patients begin to overuse nosedrops. Therefore it is hard to determine whether pathological findings in the physiology or the histology of the nasal mucosa are due to the underlying nasal disorder or if the pathology is due to the overuse of decongestants. In previous studies and in clinical practice it has been found that common reasons for beginning to overuse nasal decongestants include allergic rhinitis, vasomotor rhinitis, chronic sinusitis, pregnancy, nasal polyps or the common cold [1,2]. Even if all these conditions cause nasal obstruction, it has been shown that the abuse of nasal decongestants *per se* causes nasal blockage [3,4] or aggravation of an already existing nasal obstruction [5].

It has been suggested that rhinitis medicamentosa may be

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due to high local concentrations of α-adrenergic agonists which reduce the sensitivity of the α-adrenergic receptors impairing the vasoconstrictor ability of the nasal mucosal vessels, in response not only to topical adrenoreceptor agonists, but also in response to endogenous noradrenalin. It has been shown that the nasal mucosa has a reduced response to sympathetic nerve activation after pretreatment with an α-receptor agonist [6]. Thus, a loss of α-adrenergic tone will persist so long as the patient continues to use nasal vasoconstrictors. Regardless of the underlying nasal disease, it is essential to stop the overuse of vasoconstrictor, so that the nasal mucosa can recover. In clinical practice various methods to stop the overuse have been tried. Most authors discontinue the vasoconstrictors immediately and completely, while others recommend vasoconstrictor withdrawal from one nostril at a time [1,7]. Nocturnal sedation has also been recommended during the withdrawal process, since nasal obstruction at night interferes with sleep. The most commonly used and, according to some authors [8], most effective treatment is intranasal steroids and/or systemic steroids. However, the different treatments have never been evaluated in studies, and it has been suggested that no special treatment, except vasoconstrictor withdrawal, is needed in rhinitis medicamentosa [9].

The main aim of this study was to investigate whether fluticasone propionate aqueous nasal spray is more effective than the corresponding placebo aqueous nasal spray in the treatment of rhinitis medicamentosa. A further aim was to study whether withdrawal of the topical vasoconstrictors without active drug is sufficient treatment for these patients.

Material and methods

Study design

The study was designed as a parallel randomized, double-blind trial. Two groups with 10 patients having rhinitis medicamentosa in each group (Table 1), stopped their overuse of nasal vasoconstrictor spray immediately and were treated with either fluticasone propionate nasal spray or placebo nasal spray once daily for 14 days. Nasal mucosal swelling, as measured with rhinostereometry, acoustic rhinometry and the peak inspiratory nasal airflow

Table 1. Patient characteristics in the fluticasone group and placebo group

Patients	Age	Allergy test	Time of use (years)	Reason for starting	Drug	Doses/day	Other medication
Fluticasone group							
1. Female	28	-	3	Common cold	Oxymetazoline	2–5	
2. Female	23	-	4	Common cold	Oxymetazoline	2–10	Citalopram
3. Female	29	-	4	Unknown	Xylometazoline	3–5	
4. Female	28	-	4	Unknown	Oxymetazoline	3–4	
5. Female	31	Dog	10	Unknown	Xylometazoline	7–10	
6. Female	37	-	3	Pregnancy	Oxymetazoline	8–15	
7. Female	38	*	5	Unknown	Oxymetazoline	3–5	Omeprazole
8. Male	35	-	4	Unknown	Oxymetazoline	6–7	
9. Male	29	Cat	10	Unknown	Oxy-,xylometazoline	1–2	
10. Female	30	-	15	Unknown	Oxy-,xylometazoline	10–15	
Placebo group							
1. Male	39	-	4	Common cold	Oxymetazoline	3–4	Citalopram
2. Male	41	Cat	5	Unknown	Xylometazoline	3–4	
3. Female	39	-	7	Pregnancy	Oxymetazoline	7–8	
4. Male	32	-	7	Common cold	Xylometazoline	3–4	
5. Female	34	-	10	Pregnancy	Xylometazoline	5–6	
6. Female	38	-	6	Sinusitis	Xylometazoline	3–5	
7. Male	35	-	10	Unknown	Oxymetazoline	4–5	Paroxetin
8. Femlae	22	Birch	5	SOM**	Oxymetazoline	6–8	
9. Male	40	-	7	Unknown	Xylometazoline	3–5	
10. Male	48	-	6	Rhinoplasty	Oxymetazoline	3–4	

*House dust mite, **secretory otitis media

rate (PNIF), as well as symptom scores of nasal stuffiness, were recorded before, during and after treatment.

On the first day of the study, day 0, the patients were not allowed to use any decongestant nasal spray. After an acclimatization period of 30 min, the position of the nasal mucosa of the inferior concha in both nasal cavities was recorded repeatedly to establish the baseline mucosal position with rhinostereometry. In the same sitting position the minimal cross-sectional area (MCA 2) was then recorded with acoustic rhinometry, immediately followed by three measurements of the PNIF. The first dose of study drug was taken after the completion of the nasal measurements on day 0, but patients were instructed not to use any decongestants. After 6 days on the study drugs (day 7), the baseline positions of the nasal mucosa, MCA 2 and PNIF were measured in the same way as before. After 13 days on the study drugs (day 14), the measuring procedure was repeated. Throughout the 2 weeks of medication, each subject filled in a diary card where nasal stuffiness was estimated on a visual analogue scale in the mornings and in the evenings of each day, the first time being in the evening of day 0. The scale ranged from 0 (nose completely clear) to 100 (nose completely blocked). Written informed consent was obtained from all patients before any procedure was performed. The study was approved by the local Ethics Committee and the Medical Products Agency.

Subjects

Twenty volunteers, 12 women and 8 men, mean age 33 yr, entered the trial. All of them had overused topical decongestants for at least 2 yr, using their spray 1–15 times a day (Table 1). The skin test Soluprick® (ALK, Denmark) that was performed on all patients, showed that five of them were allergic (Table 1). The skin test contained the following allergens: birch, hazle, timothy, mould (*alternaria*, *cladosporium*), house dust mite (*D. pteronyssinus*, *D. farinae*), cat, dog, horse, rabbit, guinea-pig. On rhinoscopy, no signs of a structural basis for the nasal symptoms were noted. All patients were selected from the outpatient department of the ENT clinic at Södersjukhuset, Stockholm. They were informed that the vasoconstrictors were mainly responsible for their nasal blockage and they were urged to stop using the nose drops immediately.

Measuring methods

The nasal mucosal swelling was recorded with rhinostereometry, acoustic rhinometry and the peak inspiratory flow meter. Rhinostereometry is an optical, direct, non-invasive method for measuring nasal mucosal swelling with a high degree of accuracy. A surgical microscope is placed on a micrometer table fixed to a frame. The microscope is movable in three angular directions, establishing a three-dimensional co-ordinate system. The subject is fixed exactly to the apparatus by a plastic, individually-made tooth splint. The eye-piece has a horizontal millimetre scale. The nasal cavity is viewed through the eyepiece. Since the microscope has a small depth of focus, changes in the position of the mucosal surface of the medial side of the head of the inferior concha are registered in the plane of focus along the mm scale. The accuracy of the method is 0.2 mm [10].

Acoustic rhinometry produces an acoustic pulse which enters the nose via a tube equipped with a nose-adapter tightly adapted to the nostril. Changes in the cross-sectional area are digitized by a computer and numerical values of the cross-sectional area are registered. The minimal cross-sectional area, MCA 2, is that cross-sectional area between the anterior portions of the concha inferior and the septum. This method has been described elsewhere [11] and in previous studies it seems to have been accurate [12]. The apparatus used in this study was a RHIN 2100 (S.R Electronics APS, Lynge, Denmark).

The peak nasal inspiratory airflow rate, PNIF, was measured with a Youlten meter (Clement Clark International, Harlow, Essex, England). It consists of a rubber mask placed over the nose during inspiration, and the flow is then recorded. At the time of each recording, the subjects inhaled maximally three times and the mean of the three recordings was registered. This method has also been described elsewhere [13] and it seems to be as reliable as rhinomanometry [14].

Study drugs

All groups sprayed two puffs of the aqueous nasal spray into each nostril every morning. One group was randomized for treatment with Flutide Nasal® fluticasone propionate aqueous nasal spray 50 μg/spray puff giving a total of 200 μg a day. The other group received placebo aqueous nasal spray (vehicle). The study drugs were supplied by Glaxo Wellcome AB, Mölndal, Sweden.

Statistical analyses

Trends and spread were analysed using the mean and standard deviation. For further statistical analyses, the Student's paired and unpaired *t*-tests were employed. In calculating the mucosal swelling, the baseline position recorded on the first day was considered as a reference position and was set at zero. The changes in the mucosal positions in each side of the nose, after 2 weeks on the nasal sprays, were added and divided by two.

Results

All patients denied using any decongestant nasal spray or

other drugs affecting the nasal mucosa during the study period. All patients completed the study. The results from one patient were excluded because of a concurrent common cold during the study period.

The fluticasone group

After 1 week of treatment, the mean mucosal swelling was reduced as measured with rhinostereometry, acoustic rhinometry and PNIF. The mean reduction with rhinostereometry was −1.5 mm, compared to the recordings before treatment ($P < 0.001$). The corresponding mean increase in MCA 2 as measured with acoustic rhinometry was 0.26 cm^2 and $P < 0.001$. The PNIF measurements showed a mean improvement of 106 L/min and $P < 0.001$. Symptom scores of nasal stuffiness in the mornings were reduced by 42 ($P < 0.01$), and in the evening the corresponding reduction was 33 ($P < 0.05$). After 2 weeks of treatment, the mean reduction with rhinostereometry was −1.2 mm as compared to recordings before treatment ($P < 0.01$). The corresponding mean increase in MCA 2 was 0.27 cm^2 ($P < 0.01$). The PNIF measurements showed a mean improvement of 121 L/min ($P < 0.001$). Symptom scores in the mornings were reduced by 45 ($P < 0.01$), and the corresponding reduction in the evenings was 37 ($P < 0.05$).

The placebo group

After 1 week of treatment, the mean mucosal swelling was reduced, as measured with rhinostereometry, acoustic rhinometry and PNIF. The mean reduction with rhinostereometry was −0.6 mm which was significant compared to the recordings before treatment ($P < 0.001$). The corresponding mean increase in MCA 2, as measured with acoustic rhinometry, was 0.1 cm^2 and was not significant ($P = 0.17$). The PNIF measurements showed a mean significant improvement of 102 L/min ($P < 0.01$). Symptom scores of nasal stuffiness in the mornings were reduced by 17, which was not significant ($P = 0.07$), and in the evenings the reduction was 24 ($P < 0.05$).

After 2 weeks of treatment, the mean reduction with rhinostereometry was −0.9 mm, which was significant, compared to the recordings before treatment ($P < 0.01$). The corresponding mean increase in MCA 2 was 0.01 cm^2, which was not significant ($P = 0.8$). The PNIF measurements showed a mean improvement of 123 L/min ($P < 0.01$). Symptom scores in the mornings were reduced by 26 ($P < 0.01$), and in the evenings the reduction was 23 ($P < 0.05$).

Comparison between fluticasone propionate and placebo

There was a significantly greater improvement in the fluticasone group after 1 week and also after 2 weeks. After 1 week of treatment, a comparison between fluticasone and placebo showed a mean difference with rhinosterometric measurements of 0.9 mm ($P < 0.01$) (Fig. 1), with acoustic measurements 0.16 cm^2 ($P = 0.056$) (Fig. 2) and PNIF −8 L/min ($P = 0.8$) (Fig. 3). After 2 weeks of treatment, a comparison between fluticasone and placebo showed a mean difference with rhinosterometric measurements of 0.3 mm ($P = 0.37$) (Fig. 1), with acoustic measurements 0.25 cm^2 ($P < 0.01$) (Fig. 2) and PNIF 5 L/min ($P = 0.8$) (Fig. 3). There were no significant differences between the two treatments, concerning the symptom scores, but the symptom scores were significantly improved on the fourth day of treatment in the fluticasone group in estimates both in the mornings ($P < 0.01$) (Fig. 4) and in the evenings ($P < 0.05$) (Fig. 5). The placebo group, however, was not significantly improved until the ninth day in the mornings ($P < 0.05$) (Fig. 4), and on the seventh day, in the evenings ($P < 0.05$) (Fig. 5).

Discussion

This study shows that the mucosal swelling was reduced

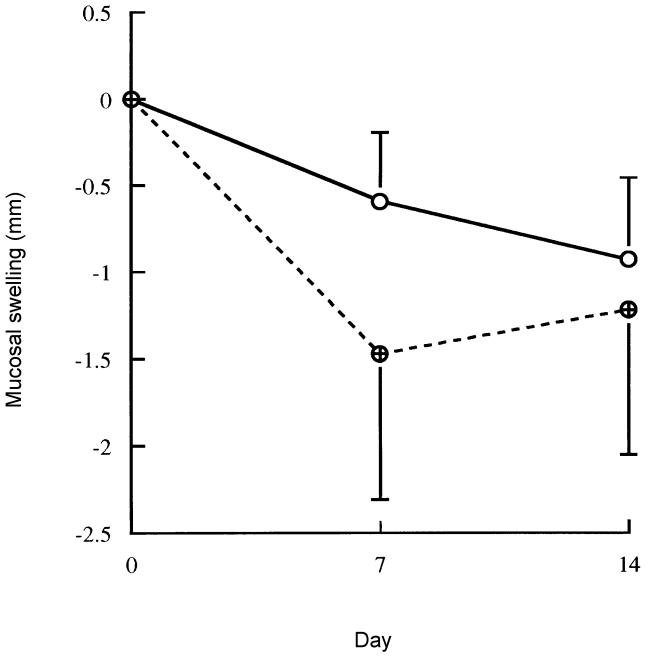

Fig. 1. Mucosal swelling (mean ±SD), as measured with rhinostereometry, during a treatment period of 2 weeks with fluticasone propionate (⊕) or placebo (○). Measurements are made on days 0, 7 and 14. The recordings on day 0 are considered the baseline position of the nasal mucosa and are set at zero. The decrease in mucosal swelling is significantly greater in the fluticasone group on the seventh day ($P < 0.01$), but not on the fourteenth ($P = 0.37$)

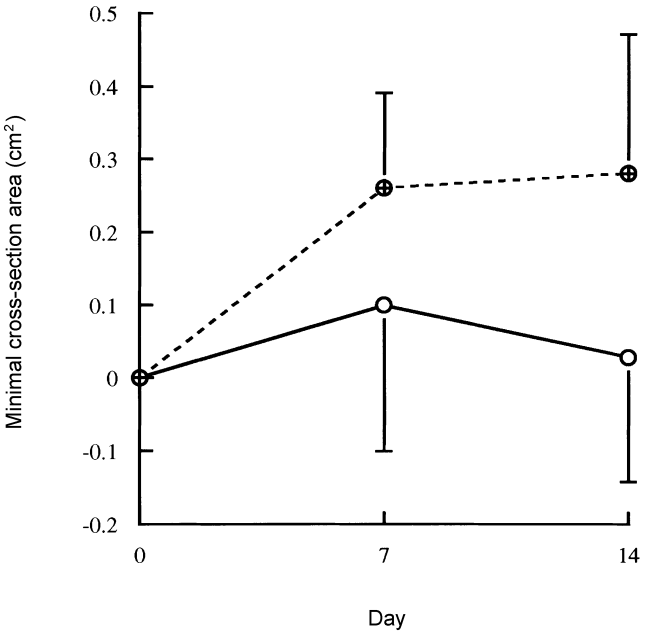

Fig. 2. The minimal cross-sectional area; MCA2 (mean ±SD), as measured with acoustic rhinometry during a treatment period of 2 weeks with fluticasone propionate (⊕) or placebo (○). Measurements are made on days 0, 7 and 14. The recordings on day 0 are considered the baseline of the MCA2 and are set at zero. The increase of MCA2 is not significantly greater in the fluticasone group on the seventh day ($P = 0.056$), but on the fourteenth day ($P < 0.01$)

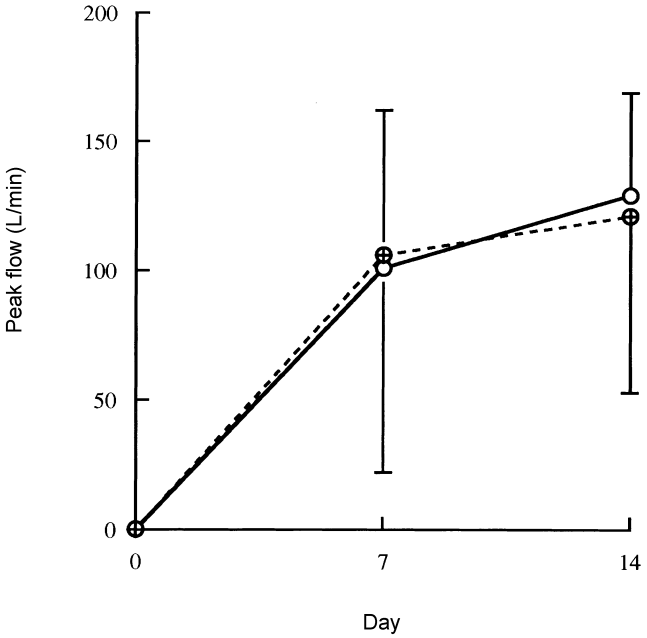

Fig. 3. Peak nasal inspiratory flow; PNIF (mean ±SD), as measured with the Youlten meter during a treatment period of 2 weeks with fluticasone propionate (⊕) or placebo (○). Measurements are made on days 0, 7 and 14. The recordings on day 0 are considered the baseline peak flow and are set at zero. There is an increase of PNIF in both groups without any significant differences on any day.

after 7 and 14 days of treatment with fluticasone propionate as well as placebo, but the reduction was significantly greater after treatment with fluticasone propionate. The symptom scores for nasal stuffiness showed a marked reduction during the treatment period in both groups, but there was an earlier onset of symptom reduction after treatment with fluticasone propionate.

An abrupt cessation of topical decongestants in patients with rhinitis medicamentosa induces marked nasal blockage because of rebound congestion [15]. The pronounced nasal obstruction is hard to endure and therefore patients often start using the decongestants again after only a few days of withdrawal. This is why treatment of rhinitis medicamentosa often fails. The first few days are crucial and our results show that fluticasone propionate reduces nasal stuffiness significantly as early as 4 days of treatment, unlike placebo, where symptom relief was not observed until 7 days. In fact, a marked reduction in symptom scores occurred during the first 3 days of treatment with fluticasone propionate. This is in agreement with clinical practice, where our impression is that patients, despite years of vasoconstrictor overuse, when they are given topical cortiocosteroids note a very fast reduction of the worst symptoms of nasal stuffiness, i.e. within 3 to 7 days. It is of great importance for successful treatment and compliance to inform patients about this fast recovery. The rapid onset of action after treatment with fluticasone propionate once daily has also been reported in the treatment of allergic rhinitis [16]. In that study, the mean total symptom score was also significantly reduced by day 4 of treatment.

This study shows that vasoconstrictor withdrawal without treatment with active drug reduces nasal mucosal swelling and symptom scores after 7 days of treatment and that no one used topical decongestants during the study period. Thus, the main aim of treatment was achieved even in the patients treated with a placebo nasal spray. However, this does not automatically mean that, in clinical practice, patients with rhinitis medicamentosa will succeed in withdrawing the vasoconstrictors without any treatment except the instruction to discontinue the decongestant which has been suggested [9]. In this study, all patients naturally hoped that they had been given fluticasone propionate. They also received special attention and much more information about the disease than they would have been given on a regular visit to our outpatient department. Moreover, it has been suggested that placebo aqueous nasal spray *per se* may have a positive effect on rhinitis medicamentosa [17]. Finally, it should be pointed out that the patients in the placebo group

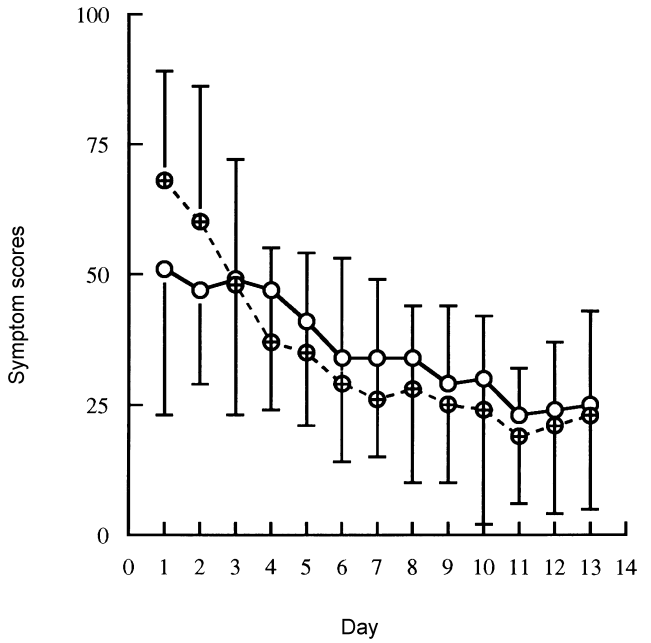

Fig. 4. Symptom scores (mean ±SD), as estimated in the mornings before the administration of fluticasone propionate (⊕) or placebo (○), during 2 weeks of treatment. The placebo group had lower symptom scores at the start, with a slow decrease of the scores during the treatment. The fluticasone group had higher symptom scores at the start, but had a rapid decrease from the first day, and the decrease was significant already on the fourth day ($P < 0.01$).

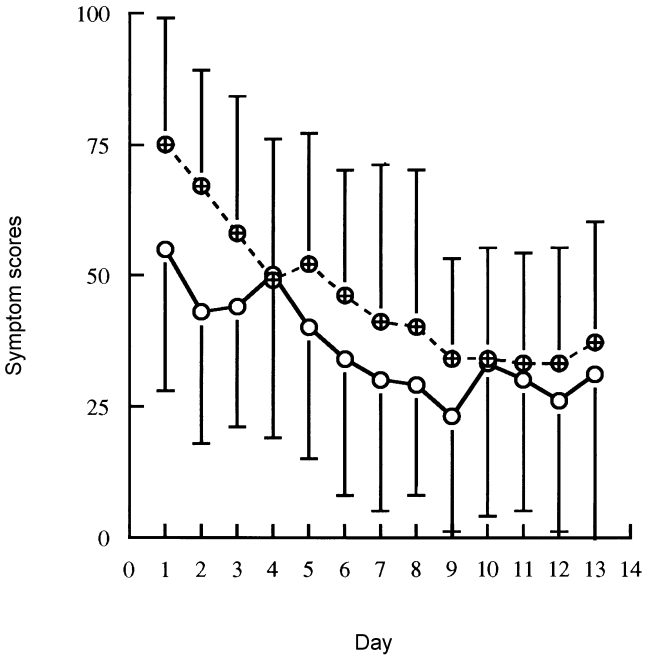

Fig. 5. Symptom scores (mean ±SD), as estimated in the evenings during 2 weeks of treatment. The placebo group had lower symptom scores at the start, and a slow decrease during the first 4 days, while the fluticasone group had higher symptom scores at the start, but had a rapid decrease from the first day, and the decrease was significant already on the fourth day ($P < 0.05$).

had lower symptom scores for nasal obstruction to start with than the patients treated with fluticasone propionate.

Rhinostereometry has been used in studies on rhinitis medicamentosa [18] and induced rebound congestion in healthy subjects previously [3,4]. The method has been useful in observing small changes in nasal mucosal swelling. Acoustic rhinometry has also been used in many studies and both methods were of value in detecting the positive effects of treatment with fluticasone propionate in this study. The PNIF recordings showed no difference between the two groups although it has been reported that this method seems reliable [14]. In this study too, PNIF seems to be reliable in recording large changes during the treatment period, but not accurate enough to detect small differences between groups.

When the patients had completed the 2-week treatment, they discontinued the study medication. Three of them, however, still suffered from nasal stuffiness and were given open treatment fluticasone propionate. These three patients were followed-up, and after 1 week of treatment they no longer had nasal stuffiness. When the study codes were broken, it turned out that two of them were in the placebo treatment group and the third was the patient in the fluticasone group who had been excluded because of a common cold. The aim of the study was to follow these patients during a 2-week treatment period and they were therefore not systematically followed-up after the study period. All patients were asked to return if they developed nasal stuffiness after discontinuation of the treatment, and 4 months later none of them have yet returned.

In summary, this study shows that fluticasone propionate is more effective and has a faster onset of action than placebo in the treatment of rhinitis medicamentosa. An adequate treatment of these patients consists of a combination of vasoconstrictor withdrawal and a topical corticosteroid to alleviate the withdrawal process. It is essential for successful treatment and compliance to give the patients adequate information about rhinitis medicamentosa in general and especially about the rapid reduction in nasal stuffiness when given correct treatment. It also seems that 2 weeks of treatment is sufficient.

Acknowledgements

This study was financially supported by Glaxo Wellcome AB, Mölndal, Sweden.

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