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Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis

A randomized, single blind, parallel study

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SUMMARY

Forty-seven informed out-patients with the diagnosis seasonal rhinitis of at least two years' duration took part in a controlled single blind, double observer, parallel four-center study for the purpose to compare efficacy and tolerance of two local corticosteroid nasal sprays: flunisolide 25 µg/dose and beclomethasone 50 µg/dose. The patients received for four weeks one of the two treatments; flunisolide 50 µg in each nostril twice daily or beclomethasone dipropionate 50 µg in each nostril four times daily. The study was conducted under the Declaration of Helsinki. Patients were assessed on admission and after two and four weeks.

All patients completed the trial. The results showed that both drugs are highly effective in controlling nasal rhinitis symptoms, 21 out of 24 flunisolide treated patients and 21 out of 23 beclomethasone treated stated good to total control after four weeks' treatment during the pollen season. No statistical difference between the two could be discovered in any of the parameters measured. The only side effect recorded was mild transistory stinging in connection with application of the two different sprays. This occurred in a few patients in both groups.

The results from the study indicate that the new corticosteroid flunisolide in a dose of 100 µg × 2 is comparable to beclomethasone dipropionate 100 µg × 4 concerning efficacy and tolerance in prophylactic treatment of seasonal rhinitis.

INTRODUCTION

It is more than ten years ago since it was shown that local application of glucocorticoids in the nose and bronchi was highly effective in rhinitis and asthma patients in doses which have no significant effects on the hypothalamo-pituitary - adrenal (HPA) axis (Czarny et al., 1968).

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The efficacy of steroids in rhinitis is considered to be due to their general anti-inflammatory properties, i.e. the ability to lead to vasconstriction and reduced permeability of the capillaries in the mucosa. Stabilization of endothelial membranes has been observed, resulting in reduced release of chemical mediators (Sørensen et al., 1976). It has also been reported that corticosteroids lower the histamine level in the tissues, probably as a result of interference with the biosynthesis, and reduce the number of basophilic cells (Mygind et al., 1978; Okuda et al., 1980).

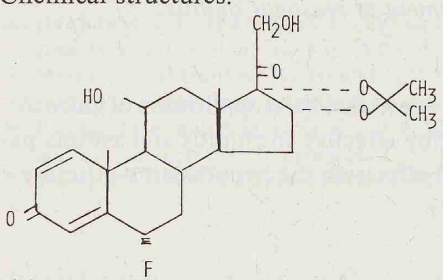
The therapy traditions in Norway have dictated a restrained use of the potent steroids because of the possible influence on the HPA axis seen after systemically active corticosteroids. Topical application of steroids has also resulted in development of atrophy in the skin, which naturally increases the cautious handling of these drugs. Steroid treatment has been reserved for difficult or diffuse rhinitis conditions, while the normal choice of drugs has been antihistamines and cromoglycate for the seasonal rhinitis patients.

In Norway, there are two steroid preparations available for local application in the nose. Beclomethasone dipropionate marketed as an aerosol, has been in use since 1974, and a long series of studies has shown that the steroid is effective in the treatment of rhinitis. Till now, systemic adverse effects of this drug has never been reported (Mygind, 1982).

Flunisolide was introduced in 1978 (and registered in Norway in 1982) as a solution in a mixture of polyethylene glycol, propylene glycol and water. It has, like beclomethasone, proved to be effective in intranasal treatment of rhinitis, and the studies have also for this drug shown no reduction of plasma cortisol level (Mygind, 1982).

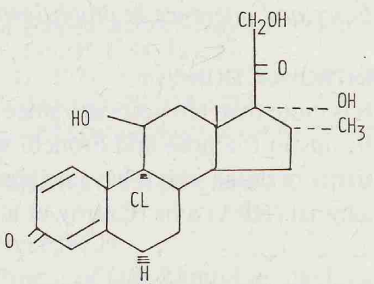
The present study was planned in attempt to elucidate more fully the place of local steroid treatment in rhinitis, especially flunisolide compared to the more established beclomethasone dipropionate, and to supplement the only study earlier comparing these two drugs (Grønås and Brydøy, 1982).

Chemical structures:



FLUNISOLIDE

Figure 1.



BECLOMETHASONE

MATERIAL AND METHODS

Forty-seven out patients of either sex aged 12 or over with the diagnosis seasonal rhinitis since at least two years entered the study. The allergy towards grass or hardwood tree pollen was confirmed by skin test and provocation test or RAST. The symptomatology, nasal stuffiness, rhinorrhea and sneezing, lasted empirically for at least four weeks. A condition for inclusion was that any other therapy which could influence the clinical pattern was stabilized.

Excluded were patients with unspecific allergy, infections in the airways, occluding nasal polyps, any malign illness, or any disease for which corticosteroid therapy was contraindicated. Pregnant or lactating women were also excluded.

The study was designed as a single blind, double observer, parallel four-center study. The patients were entered into one of the two treatment groups according to a computer-generated code randomized for each center in blocks of 12. Double observer technique was used because of different appearance of the two nasal sprays. In practice the investigator's nurse explained the use of the sprays, and handed out and collected the medication, while the investigator entered the patients and made assessments.

The patients were treated for four weeks with one of the following preparations:

A. *Flunisolide* as an aqueous solution of 0,025% flunisolide with propylene glycol and polyethylene glycol applied to the nasal mucosa by a metered pump device free of propellats (Lokilan – Astra-Syntex A/S). Each dose contains 25 µg flunisolide. The dosage was two sprays in each nostril two times a day for a total dose of eight sprays (200 µg flunisolide per day).

B. *Beclomethanose dipropionate* as a propelled aerosol (Becotide Nasal-Glaxo). Each dose contains 50 µg beclomethasone dipropionate. The dosage was one spray in each nostril four times a day for a total dose of eight sprays (400 µg beclomethasone dipropionate per day).

Eye symptoms were allowed treated with antazoline sulphate+naphazoline nitrate (Antistin-Privin-Dispersa) or sodium chromoglycate (Lomudal-Fisons) eye drops if needed.

Clinical assessments were made on admission and after 2 and 4 weeks of treatment. An ENT-examination was done, stressing nasal secretion and a visual judgement of the nasal mucosa. It was also recorded whether symptoms interfered with sleep and daily routines or not.

During the 4 weeks of treatment the patients recorded every day the severity of their individual symptoms from nose and eyes in a diary card, as well as the weather situation: Severity of sneezing, stuffiness, runny nose, and itching was graded as: none, mild, moderate, or severe. Occurrence of epistaxis was recorded using the same scale. After two and four weeks of treatment the total achievement of the test spray was evaluated as providing: total control of symptoms; good control, but not complete; minor control; no benefit; or worsening of symptoms. Any

side effects, elicited by indirect questioning, noted in the preceding two weeks were evaluated and recorded with severity and possible relationship to the test medication.

When all patients were evaluated after four weeks of treatment, the randomization code was broken and the results analysed. Different statistical methods were used for the evaluation. Variables measured on an interval scale (age) were analysed by two sample t-test, whereas variables measured on an ordinal scale were analysed by Mann-Whitney U-test (symptom score), or Wilcoxon matched pairs signed ranks test (change from baseline). Variables measured by a nominal scale (sex) were analysed by the chi-square test for two independent samples or Mc Nemar's test of changes. A significance level at 5 per cent was chosen for the analysis, and the tests are used two-tailed.

The study was conducted in accordance with the Declaration of Helsinki, and the National Centre for Medical Products Control in Norway reviewed the scientific aspects of the study before start.

RESULTS

All 47 patients who entered the study completed the four weeks of treatment; 24 in the flunisolide group and 23 in the beclomethasone dipropionate group. There was no statistical difference between the two groups on admission regarding demographics or medical history.

The nasal symptoms were significantly reduced both after two and four weeks of treatment compared to pretreatment for both flunisolide and beclomethasone dipropionate groups ($p < 0{,}001$). There was no difference between the two treatment groups, and the patients' daily recordings of symptom severity showed the same pattern. None of the patients showed a normal nasal mucosa when the treatment started, and 44 of 47 showed a congested mucosa. The congestion was significantly reduced for both groups after two and four weeks, and a full normalization of the mucosa at the end of the treatment period was achieved in 8 flunisolide patients ($p < 0{,}01$) and in 6 of the beclomethasone dipropionate treated ($p < 0{,}05$).

Nasal secretion occurred in 4/5 of the patients on admission. This number was after four weeks reduced by 11 in the flunisolide group ($p < 0{,}05$) and by 8 in the beclomethasone group ($p < 0{,}05$). Twenty-two of the 24 flunisolide and 21 of the 23 beclomethasone patients stated their rhinitis symptoms to interfere with daily routines before start of treatment. Only one flunisolide patient still complained of this after two and four weeks ($p < 0{,}01$). The corresponding number of beclomethasone patients were 1 and 3 after two and four weeks, respectively ($p < 0{,}05$). There was no significant difference between the two treatments. Sleep disturbance was

reduced in the flunisolide group from 6 patients before start to 0 at the first follow-up visit and 2 at the end of trial. The corresponding figures for the beclomethasone group were 9 at start, then 2 and 1 at the two follow-up visits. The reduction is statistically significant for both treatment ($p < 0,05$).

The patients' overall evaluation of the test medication after two and four weeks is shown in Figure 2. The physicians' opinion of the treatment show the same pattern. In the flunisolide group, 21 of 24 patients (87%) considered the test spray to result in good to total control of nasal symptoms at the end of the treatment period. Among the beclomethasone treated patients, after four weeks of treatment 21 of 23 (92%) stated that the treatment gave good to total control of their nasal rhinitis symptoms. There was no statistical difference between the treatments.

Mild nasal irritation in connection with application of the nasal sprays were reported from 7 patients during the study, 2 in the flunisolide group and 5 in the beclomethasone group. It lasted only a short while, and none of the patients concerned wanted to discontinue the treatment. No other side effects were recorded. The patients' own symptom score was tried related to the weather situation, but this was not successful.

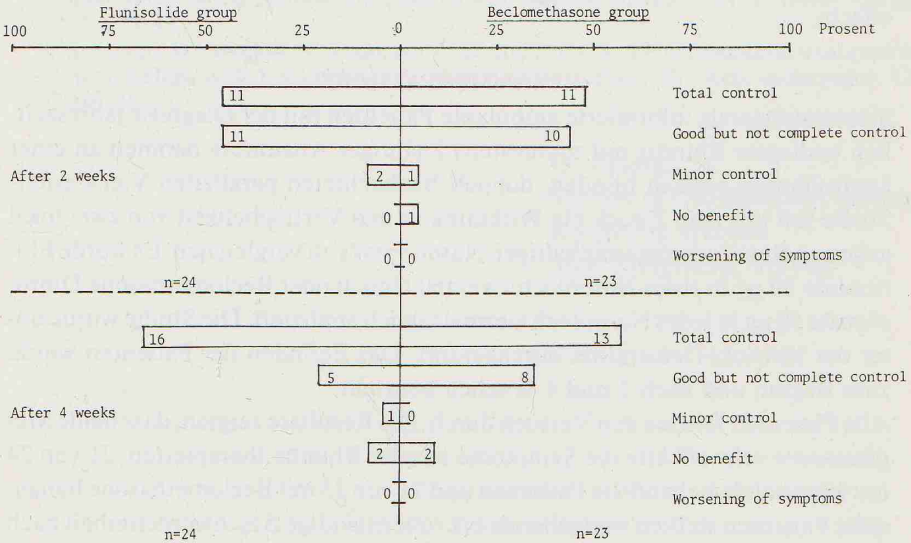


Figure 2.

DISCUSSION

From the results of this study there seem to be no statistical difference between flunisolide 100 µg twice daily and beclomethasone dipropionate 100 µg four times daily in the treatment of seasonal rhinitis. Both drugs were highly effective, and the treatments were without any troublesome side effects. The results confirm the earlier findings of Grønås and Brydøy in 1982, and other studies of both flunisolide (Strem et al., 1978), and beclomethasone dipropionate (Brown et al., 1977) in the treatment of seasonal rhinitis.

Some of the patients had in former seasons been treated with antihistamines or cromoglycate. These patients expressed preference for steroid treatment compared to these drugs regarding effect as well as side effects.

We believe that a twice daily administration of the nasal spray may be an advantage in patient compliance. This dosage has been used for flunisolide for several years, and was recently approved for beclomethasone. Flunisolide is administered by a metered pump device free of propellants which gives a constant dose as well as a very good mucosal distribution. This may offer a good alternative to the aerosol propelled beclomethasone dipropionate, as dryness of the anterior part of the nose is known to occur with aerosols (Mygind, 1978).

To get a more exact picture of the effect of the treatments, the results should perhaps have been related to the pollen counts. This was not done because the four centres were in different areas, and there is no routine pollen count service in all these districts.

As a conclusion, we consider the local nasal treatment with steroids to be a good alternative to antihistamines and cromoglycate, regarding both effect and side effects.

ZUSAMMENFASSUNG

Siebenundvierzig informierte ambulante Patienten mit der Diagnose jahreszeitlich bedingter Rhinitis mit mindestens 2 jähriger Anamnese nahmen an einer kontrollierten einfach blinden, doppelt beobachteten parallellen Vier-Center-Studie teil mit dem Zweck die Wirksamkeit und Verträglichkeit von zwei lokal angewandten Corticosteroidhaltigen Nasen sprays zu vergleichen. Es wurde Flunisolide 50 µg in jedes Nasenloch zweimal täglich oder Beclomethasone Dipropionate 50 µg in jedes Nasenloch viermal täglich appliziert. Die Studie wurde unter der Helsinki-Deklaration durchgeführt. Das Befinden der Patienten wurde zum Beginn und nach 2 und 4 Wochen beurteilt.

Alle Patienten führten den Versuch durch. Die Resultate zeigten, dass beide Medikamente sehr effektiv die Symptome nasaler Rhinitis therapierten, 21 von 24 mit Flunisolide behandelte Patienten und 21 von 23 mit Beclomethasone behandelte Patienten stellten weitgehende bis vollenständige Beschwerdefreiheit nach 4 wöchliger Behandlung während der Pollenzeit fest. Statistische Unterschiede

zwischen den beiden Gruppen konnten in keiner der untersuchten Parameter festgestellt werden. Der einzige verzeichnete Nebeneffekt war ein leichtes vorübergehendes Brennen bei der Anwendung beider Sprays. Dieses leichte Brennen kam bei wenigen Patienten in beiden Gruppen vor.
Die Resultate zeigen dass das neue Corticosteroid Flunisolide in einer Dosierung von 100 µg × 2 mit Beclomethasone Dipropionate 100 µg × 4 hinsichtlich der Wirksamkeit und Verträglichkeit bei der Behandlung jahreszeitlich bedingter Rhinitis zu vergleichen ist.

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