

A new formulation of flunisolide for intranasal application reduces side effects

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In several studies, flunisolide, a synthetic corticosteroid, used intranasally, has been documented for the treatment of perennial and seasonal allergic rhinitis (4).

In all intranasal studies with flunisolide, transient nasal irritation and stinging lasting a few seconds after inhalation is the most common side effect occurring in about one third of the patients (4). This side effect generally occurred as often as during the placebo period (4), and it is probably due to the vehicle solution.

The vehicle solution has been changed in order to reduce these side effects: propylenglycol, known to produce toxic skin reactions (5), is reduced to one fourth, and polyethylenglycol (p.e.g. 4000) has been substituted by polyethylenglycol (p.e.g. 400) and polysorbat 20.

The purpose of the present trial was to compare the new formulation with the old.

PATIENTS

Five men and 21 women between 18 and 76 years of age (median 41 years) suffering from active rhinitis (median duration 5 years, range 2–30) (defined by showing at least two or more of the following four symptoms occurring intermittently during a 2 year period: nasal blockage, runny nose, sneezing and nasal itching) (3)), had been tested by the skin prick test technique (1) with a standard allergen panel (ALK, Copenhagen, Denmark). Eight patients were positive to

one or more allergens. Eight patients also had increased levels (median 67 kIU/l, range 1–986) of specific IgE antibodies in the blood (2). Within the last 2 weeks before the study, none of the patients had received intranasal or systemic corticosteroids. One week before, treatment with antihistamines was discontinued except for the long-acting astemizole, which was withheld for 6 weeks, and treatment with antihistamines was not allowed during the study. Eight patients had bronchial asthma (median duration 5 years, range 1–30 years) and were treated with β_2 -agonists, theophylline or inhaled steroids in a fixed dose throughout the study. Patients who had received immunotherapy within 6 months prior to the study, patients with structural abnormalities in the nose, pregnant women or patients receiving medication for treatment of other diseases than bronchial asthma were not included in the study. All patients gave their informed consent to participation.

METHODS

In a double-blind cross-over design the patients were randomly allocated to two treatment groups: one treated with the old formulation of aqueous flunisolide (25 μ g per puff, 1 puff into each nostril twice daily), and one treated with the new formulation of aqueous flunisolide (25 μ g per puff, 1 puff into each nostril twice daily) delivered by metered dose nasal sprays. After 3

weeks' treatment the cross-over was performed, and each group received the alternative treatment for the final 3 weeks. The labelled identically looking nasal sprays were supplied by Syntex, Denmark. The spray technique was controlled at each visit to the clinic.

In a diary, patients recorded symptom scores (maximum 3) for sneeze, stuffy and runny nose throughout the study. The patients were actively motivated to assessing side effects of the treatment by daily recording of irritation and stinging (yes/no) immediately after application of the treatment.

We tested the pH of commonly used aqueous nasal sprays (Rhinocort Aqua® (Draco), Lomudal® (Fisons), Beconase Aqua® (Glaxo), and Locasyn Nasal® (old and new formulation) (Syntex) with Universal Indikatorpapier (pH 1-10) (Merck).

Statistics

Mann-Whitney test was used for comparing data.

RESULTS

Twenty-six patients completed the study. One patient stopped treatment with the old formulation after 1 week of treatment due to stinging and itching, and was excluded.

Both treatments proved equally effective in controlling symptoms in the doses given.

Thirteen patients had side effects during treatment with both formulations, whereas no patient experienced side effects on the new formulation only. A comparison of side effects is shown in Fig. 1.

The Mann-Whitney test demonstrated a statistically highly ($P < 0.0000$) significant difference between the number of days with side effects in favour of the new formulation.

The pH of all tested aqueous nasal sprays was 5, no differences were observed.

CONCLUSION

The new formulation of the vehicle solution for flunisolide has reduced side effects compared to

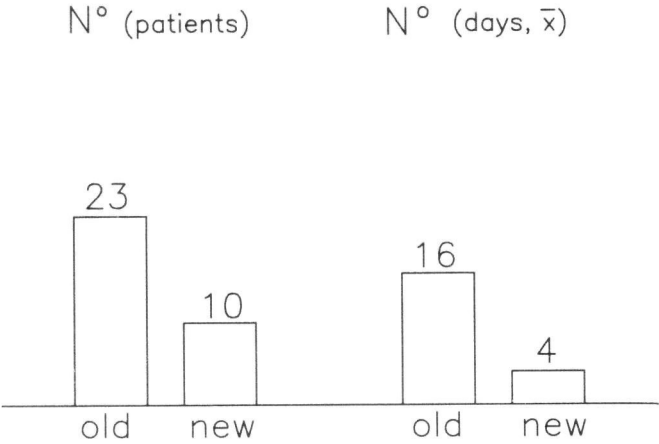


Fig. 1. The number of patients who reported side effects (stinging and itching of the nose) after application of the two formulations of flunisolide and the number of days with reported side effects.

the old formulation. Symptoms were equally effectively controlled with the two formulations. Placebo was not included, since other studies reported that side effects generally occurred as frequently with placebo as with active treatment. Acidity of the applied solutions was not mutually different or different from other commonly used aqueous nasal aerosols.

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