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Long-term effects of topical corticosteroids in the nose

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Abstract

In a prospective study, biopsies were taken from the septal mucosa in 21 patients of whom 11 had been using topical nasal corticosteroids. In contrast to the effect of long-term treatment with corticosteroids in the skin, but in accordance with previous investigations of the nasal mucosa, no histopathological changes of significance were found, although the biopsies were taken from different sites. These findings do not suggest that topically corticosteroids are harmful to the nasal mucosa.

Introduction

Topical corticosteroids have been widely used for years in the treatment of allergic rhinitis and perennial non-allergic rhinitis as well as for other nasal disorders. Many people are using topical corticosteroids continuously for months or for years. In spite of that, our clinical impression is that these drugs give rise to few side effects. Local irritation or occasional bleeding from the Kieselbach's area of the nasal septum, however, occurs frequently (Holopainen *et al.*, 1982; Lindqvist *et al.*, 1986). These side effects can sometimes be appeased by more careful administration. Continuous use of corticosteroids may induce both local and systemic adverse effects. The aim of this investigation was to evaluate any histopathological changes of the septal nasal mucosa after long-term treatment with topical corticosteroids in man.

Materials and methods

The study was performed prospectively without random allocation on 21 patients (three women and 18 men, between 18 and 67 years old; mean age 32 years), who were admitted for nasal surgery for septal deviation or nasal polyposis and who gave informed consent. Eleven of the patients had used topical corticosteroids, Budesonide dipropionate (BUD) and/or Beclomethasone dipropionate (BDP), continuously for between three and more than 36 months for perennial non-allergic rhinitis. Ten of the patients who had never used topical corticosteroids served as controls (Table I).

Biopsies, about 2 × 4 mm wide to the depth of the perichondrium, were taken after informed consent from Kieselbach's area. They were fixed in 4 per cent formaldehyde solution and stained with haematoxylin-eosin and alcoin blue-PAS. The biopsies were all examined by the same pathologist, who was unaware of the patients' treatment. The following parameters were judged:

1. Signs of inflammation (a. general, b. leukocytes (other than eosinophils), c. eosinophils).
2. Thickness of the basal membrane.
3. Fibrosis.
4. Squamous metaplasia.

The first three were judged semi-quantitatively in a scale of seven steps (0–6 where 0 = no signs and 6 = pronounced). Squamous metaplasia was judged as present or absent (±).

The statistical analyses of the observations were performed with the Mann-Whitney U-test and Fisher's exact test.

Results

There was no statistically significant difference in age between the patients who had used topical nasal steroids and those who had not. In Table II, the mean score (± SD)

TABLE I

TREATMENT (IN MONTHS) WITH TOPICAL BECLOMETHASONE DIPROPIONATE (BDP) AND/OR BUDESONIDE DIPROPIONATE (BUD) IN 21 PATIENTS WITH OR WITHOUT NASAL POLYPOSIS

Sex	Age	Polyposis	Treatment	Duration
M	67	+	BDP	2
M	58	+	BUD	5
M	53	–	–	0
M	46	+	BDP	8
M	42	–	–	0
M	39	+	BDP/BUD	>36
M	34	+	BDP	4
F	29	–	–	0
M	25	–	–	0
M	25	+	BDP/BUD	>36
M	26	–	–	0
M	27	–	–	0
F	26	–	BDP/BUD	2
M	25	–	–	0
M	24	+	BDP/BUD	>36
M	23	+	BUD	>36
M	20	–	BUD	6
M	21	–	BUD	4
M	20	–	–	0
F	19	–	–	0
M	18	–	–	0

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TABLE II

HISTOPATHOLOGICAL EVALUATION OF THE BIOPSIES TAKEN FROM THE SEPTUM OF PATIENTS TREATED WITH TOPICAL CORTICOSTEROIDS (N = 11) OR CONTROL GROUP (N = 10). NO DIFFERENCES BETWEEN THE GROUPS WERE STATISTICALLY SIGNIFICANT

	Steroid group	Control group
General inflammation	2.6 ± 1.4	3.1 ± 1.4
Leukocytes	2.5 ± 1.3	2.8 ± 0.9
Eosinophils	1.6 ± 1.7	0.9 ± 1.4
Thickness of basal membrane	3.0 ± 1.6	2.7 ± 1.7
Fibrosis	2.5 ± 1.4	2.8 ± 1.4
Epithelial metaplasia	n = 6	n = 7

of the findings in the nasal mucosa is plotted with the frequency of epithelial metaplasia. No significant differences were found between the groups.

In additional calculations, analysis of variance was performed to evaluate possible differences in histopathological patterns depending on different period of treatment with topical nasal corticosteroids. No significant differences were found.

Discussion

Topically administered potent corticosteroids are well known to induce atrophy of the skin after long-term use (Stefanovic, 1972). During the last decade, several investigations have shown that skin atrophy occurs after only two to three weeks treatment with different kinds of corticosteroids (Somerma *et al.*, 1984; Serup and Holm, 1985; Pierard *et al.*, 1989). Therefore, the duration of treatment should not be a limiting factor in this study. In nasal mucosa, however, no atrophy has been reported in spite of the widespread use of these drugs (Poynter *et al.*, 1977; Mygind *et al.*, 1978; Klemi *et al.*, 1980; Sahay *et al.*, 1980; Holopainen *et al.*, 1982; Pipkorn and Berge, 1983; Lindqvist *et al.*, 1986; Pipkorn *et al.*, 1988). Since the reasons for this discrepancy are unknown, the present study, using material from a hitherto not studied nasal area namely nasal septum, seemed well motivated.

After topical treatment with BDP no mucosal atrophy has been found but a significant decrease in the number of eosinophils has been observed (Poynter, 1977; Mygind *et al.*, 1978; Klemi *et al.*, 1980; Holopainen *et al.*, 1982). No sign of atrophy in the nasal mucosa was found after flunisolide nasal spray (Sahay *et al.*, 1980). The effect of topical BUD before and after one year in patients with perennial rhinitis has been investigated and shown to produce no significant morphological change (Pipkorn and Berge, 1983; Lindqvist *et al.*, 1986). In a follow-up study, additional biopsies were taken after 2.5 and 5.5 years, still without finding any significant histopathological changes in the nasal mucosa (Pipkorn *et al.*, 1988).

Previous investigations of the long-term effects of topical corticosteroids in the nose have all been performed with biopsies taken from the inferior turbinate or from nasal polyps. These samples are very easy to take under local anaesthesia, because the nasal mucosa is thickest over the inferior turbinate (Cauna, 1982). It is tempting to assume that, if any morphological changes were to appear, they would be seen on the Kieselbach's triangle of the septum, where the mucosa is very thin and firmly attached to the perichondrium (Cauna, 1982), and where bleeding and crusting can be found as an adverse effect of topical corticosteroid treatment. Biopsies from Kieselbach's area, however, are difficult to take. Therefore, when planning this study, we decided to take the biopsies from patients who were undergoing surgery under a general anaesthetic. A disadvantage was that biopsies could not be taken before the treatment period and the patient sample studied was very small.

Why is nasal mucosa more resistant to corticosteroids than squamous epithelium of the skin? One explanation could be that the much higher blood flow in the nasal mucosa might protect the mucosa (Bende, 1983). A high blood flow is known to be accompanied by an increased turnover of drugs and an increased ability to heal mucosal wounds. The lack of histopathological atrophy of nasal polyps (Mygind *et al.*, 1978) is against this theory, however, since the blood flow in nasal polyps is as low as that in the skin (Bende and Flisberg, 1985).

Another explanation for the different reaction between nasal mucosa and skin is a possible effect of the mucociliary system of the nose. Corticosteroids might rapidly be removed by the cilia and thus not remain on the mucosa long enough to induce damage. Corticosteroids, as evaluated for BUD (Lindqvist *et al.*, 1989), seem to penetrate well into the mucosa and have their main effect topically. In spite of that they are rapidly found in the systemic circulation without binding to the nasal mucosa after nasal administration (Åkerlund *et al.*, 1991).

Thus, there were no trends towards squamous metaplasia or thinning of the basement membrane, which would indicate the beginning of atrophy. The lack of any signs of mucosal atrophy after treatment contrasts with dermal findings (Stefanovic, 1972), but it is in accord with previous nasal mucosa investigations.

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