EFFECTS OF BECLOMETHASONE DIPROPIONATE AEROSOL ON NASAL MUCOSA

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Rhinoscopic examination and histological studies of the nasal mucosa in patients with perennial allergic rhinitis and nasal polyposis treated with beclomethasone dipropionate aerosol provided no evidence that this form of treatment, given for one year, produced any harmful effects, such as atrophic rhinitis.

Introduction

Several placebo-controlled trials have demonstrated the efficacy of intranasal beclomethasone dipropionate aerosol (BDA) in the treatment of hay fever, perennial allergic rhinitis (PAR) and nasal polyposis (Brodgen *et al.*, 1975; Mygind, 1977). This does not imply that further studies of this therapy are without interest, since many questions still remain to be answered. Amongst these are problems of drug distribution, selection of patients for therapy and, most important, the mode of action of a potent corticosteroid on the airway mucosa and the potential risk of local side-effects.

The nose is a suitable target for such studies, partly because the nasal mucosa, as compared with the bronchial mucosa, is exposed to relatively large amounts of corticosteroid, and partly because the nasal mucosa can be inspected directly, and samples of secretion and serial biopsies readily obtained. The almost identical histological structure of the nasal and bronchial mucosa also permit extrapolation of some of the findings from the nose to the bronchi.

In an attempt to elucidate some of the outstanding problems defined above we present the results of four years' experience with the intranasal use of BDA. For further details, the reader is referred to Sorensen *et al.* (1976), Mygind *et al.* (1977) and Mygind (1977).

Methods

Since 1973, 117 patients have participated in placebo-controlled studies of intranasal BDA in the treatment of hay fever, PAR and nasal polyposis, and a larger number has been assessed in open studies. The most valuable information has been obtained from a 9–30 months' continuous assessment of 33 patients with nasal polyposis, from whom serial mucosal biopsies were taken and examined, without previous

knowledge of their source, by light and scanning electron microscopy. In addition, nasal smears were taken for semiquantification of eosinophils; secretions were collected for measurement of IgA, IgG, IgE and albumin; and material from nasopharyngeal swabs was cultured for bacteria and fungi. A plastic cast of the human nose was used for the study of intranasal BDA distribution, which was visualized by toluidine blue delivered from a pressurized aerosol canister. Similarity between dye and drug distribution was ensured by McKinzie skin blanching tests, using eluents from different areas of the nasal cast treated with BDA (Mygind & Vesterhauge, 1977).

Results and Discussion

Nasal irritation

Patients with PAR react readily with sneezing to many non-specific stimuli, suggesting increased sensitivity of the nasal irritant receptors. Some of our patients reacted initially with nasal irritation to the intranasal administration of the freon-propelled BDA. This reaction, as well as the patients' spontaneous sneezing attacks, almost disappeared after BDA treatment had been given for a few days. In an indirect way, this indicates that the corticosteroid drug may act partly by reducing the non-specific reactivity of nasal irritant receptors. Further investigation of the nature of these surface receptors, and the way in which their reactivity can be altered by disease and by therapeutic agents is, however, clearly required.

Secretory activity

One of the beneficial effects of BDA is the marked

Figure 1 Distribution of a topically applied drug on the lateral wall and septal wall (lower part of the figure) in a model of the human nose. The drug (toluidine blue) was delivered from a Becotide inhalor equipped with a nasal adaptor. It is obvious that most of the drug hit the mucous membrane 'like a bullet from a gun'; large doses are applied to the anterior part of the septum and the tips of the turbinates. Beconase gives almost an identical drug distribution. It might be a consequence of the study (Mygind & Vesterhauge, 1977) that the cannister has to be held strictly in the sagittal plane and that one puff in the upper as well as one puff in the lower part of the nose twice a day should be the recommended practice.

reduction in nasal hypersecretion. Presumably because of the uneven mucosal drug distribution, with a relatively large amount lodging in the anterior part of the nose (Figure 1), a few patients complained of an unpleasant dryness in this part of the nose, although the large majority regarded it as a pleasant change from a constant wet and dripping nose.

Light microscopy examination of nasal polypi showed a significant reduction in the number of goblet cells after BDA treatment for one year (Figure 2). This is probably an indirect result of the increased nasal patency (Mygind *et al.*, 1974a), but an alternative possibility is that the topical application of large doses of a potent corticosteroid may alter goblet cell kinetics and/or secretory capacity. This would be consistent with the reduction of nasal hypersecretion in the treated PAR patients. Such a mode of action of long-term therapy would add a further dimension to the topical use of BDA, but may also imply a risk of local side-effects. Further studies to establish whether BDA can directly affect the number of goblet cells,

Figure 2 Number of goblet cells in nasal epithelium before (□) and after (△) BDA treatment for 9–12 months.

and whether this is reduced to a subnormal level during treatment, are now in progress.

Blood vessels

The increased nasal patency after a few days of treatment is possibly due to vasoconstriction, especially of the large turbinate sinusoids. Although unproven, it seems likely that corticosteroids enhance the α -adrenergic reactivity of the smooth muscle cells of nasal blood vessels in the same way as they potentiate the β_2 -adrenergic reactivity of bronchial smooth muscle. The amount of tissue oedema in nasal polypi decreased significantly, but very slowly, during longterm BDA therapy (Table 1). The concentration of plasma proteins in nasal fluid also decreased (Table 2), indicating that the epithelial as well as the endothelial barrier was stabilized by BDA. Some patients had daily episodes of slight blood-staining of nasal secretion for a few days after treatment was started, but this was not a problem during long-term treatment. This phenomenon seemed to be related to mucosal dryness in the anterior part of the septum. In no case was frank epistaxis associated with corticosteroid treatment. Histological examination did not reveal any perivascular bleeding after treatment but our histological technique was not suitable for the study of blood vessel ultrastructure.

Eosinophil leucocytes

The number of eosinophils in polyp tissue decreased significantly during long-term BDA treatment (Figure 3), but the fall in the number of smear eosinophils (after treatment for 3 weeks) was slight and insignificant. The discrepancy between these findings may in part be explained by the fact that the biopsies were taken from an area of mucosa heavily exposed to the corticosteroid aerosol, whereas the smears consisted of material collected from all parts of the nasal lining. A close relationship between local eosinophilia and a good response to corticosteroid therapy was

suggested, but not yet proven, by serial observations. A further discussion of this 'cell of beauty and mystery' is beyond the scope of this article.

Surface epithelium

Atrophic rhinitis is characterized by an abnormally increased nasal patency, with subsequent squamous cell metaplasia of the surface epithelium and crust formation, which extends to the posterior part of the nasal cavity. A single mucosal biopsy, examined by light or scanning electron microscopy, is usually adequate for diagnosis (Holapainen, 1965; Mygind *et*

Table 1 Results of blind microscopy of nasal polyp tissue before and after BDA treatment for one year

	Means of pre-treatment values	Means of post-treatment values	Wilcoxon Sign Rank Test
Light microscopy scores for surface epithelium	61.8	61.2	$P > 0.1$
Scanning electron microscopy scores for surface epithelium	53.4	52.8	$P > 0.1$
Degree of tissue oedema (+ = 1, ++ = 2, +++ = 3)	2.4	1.6	$P < 0.05$
Number of tissue eosinophils/mm ²	207.0	110.0	$P < 0.02$
Number of goblet cell/mm	84.8	42.3	$P < 0.01$

Each biopsy was given a score for surface epithelium from 0 (horny desquamating epithelium) to 100 (ciliated epithelium)

Table 2 Concentration of proteins in nasal secretions from patients with nasal polypi before and after BDA treatment for one year compared with matched normal control persons (from Sorensen *et al.*, 1976)

		Number of patients	Median (mg/100 ml)	25-75 Percentile (mg/100 ml)	Mann Whitney Rank-Sum Test
Albumin	Before treatment	12	450	130-920	$P > 0.01$
	After treatment	20	124	67-720	
	Normal controls	29	56	45-120	
IgG	Before treatment	14	180	57-255	$P < 0.01$
	After treatment	19	38	18-89	
	Normal controls	29	28	15-46	
IgA	Before treatment	13	75	28-165	No significant difference
	After treatment	21	73	35-283	
	Normal controls	29	78	58-118	
IgE	Before treatment	16	68*	31-366	$P < 0.01$
	After treatment	19	21	12-125	
	Normal controls	33	(5)	<5-12	

* All IgE values are IU/ml.

Figure 3 Number of eosinophils in polyp tissue before (□) and after (△) BDA treatment for 9–12 months.

al., 1974b). The main aim of our long-term biopsy study was to discover any early signs of atrophic rhinitis during BDA treatment. In addition to histological examination, anterior rhinoscopy was carried out repeatedly, and patients were questioned about symptoms such as crusting in the back of the nose.

None of the investigations showed squamous cell metaplasia or atrophic rhinitis (Table 1). In a few patients, a single crust was seen on the tip of the inferior turbinate or on the front of a polyp. This phenomenon was probably related to treatment, since untreated patients with wet and blocked noses seldom develop crusts in the anterior part of the nose, but it can hardly be regarded as an adverse effect of treatment.

Long-standing nasal polypi may widen the nasal cavity and in some cases even break the naso-maxillary suture, changing the normal slit-like cavity into a tube, with impairment of nasal function and subsequent risk of development of squamous cell metaplasia. Thus, any effective treatment of the more

severe cases of nasal polyposis will be a matter of delicate judgement. In the author's opinion, BDA therapy combined with simple polypectomy will, in most cases, be more satisfactory than radical surgery, such as ethmoidectomy.

Resistance to infection

It is difficult to assess the incidence of upper airway infection in patients with PAR, but there is no evidence that treatment with BDA for some years increases the frequency or aggravates the course of upper airway infections. Indeed, some patients in our long-term study stated that the periods of purulent rhinosinusitis, which they usually experienced following common colds, were shortened after they started BDA treatment. This could be related to increased nasal patency and improved drainage from paranasal sinuses. Examination of nasal secretions did not show any increased number of pathogenic bacteria or fungi after treatment (Malm & Wihl, 1975; Sorensen *et al.*, 1976), and no reduction in secretory IgA levels were observed (Table 2).

Conclusions

Several placebo-controlled studies have confirmed the efficacy of intranasal BDA in the treatment of hay fever, PAR and nasal polyposis; in clinical practice this drug has already established its position as one of the most effective measures in the management of nasal allergy. Extensive use and controlled observations over a period of several years have shown that continuous use of intranasal BDA is not associated with a significant risk of local side-effects, as might have been expected on the basis of dermatological experience. Although our studies of local side-effects have so far been negative, it is hardly justified to claim that no risk exists. Further studies are required, especially in children, as we have no evidence that prolonged BDA treatment, started early in life, may not affect the development of mucosal immunity or structure. In adults, it is our policy to recommend continuous BDA treatment in all patients who seem likely to benefit from it. If the nasal mucosa is regularly inspected, we feel this form of treatment is safe and in the patient's best interest.

I thank Mr D. Rhodes, Allen & Hanburys Research Limited, for the supply of aerosol canisters containing toluidine blue.

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