

Other anti-inflammatory uses of intranasal corticosteroids in upper respiratory inflammatory diseases

Topical corticosteroids are an effective treatment for nasal polyposis and other conditions associated with rhinitis. There is evidence that asthma, otitis media with effusion, and acute sinusitis may all benefit from such therapy. Fluticasone propionate (FP) drops have been shown to reduce polyp size, and to improve nasal inspiratory flow, while avoiding the side-effects of, for example, topical betamethasone therapy. In small children with allergic rhinitis, fluticasone propionate aqueous nasal spray (FPANS) has been shown to be significantly more effective than ketotifen in relieving night and daytime symptoms, and nasal blockage. There is also preliminary evidence of efficacy in obstructive sleep apnoea and acute sinusitis. The advent of FP, with its low propensity to cause systemic side-effects, makes it possible to use topical corticosteroid therapy safely for prolonged periods to treat many inflammatory diseases of the upper respiratory tract.

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Introduction

It is becoming recognised that corticosteroids are an effective treatment for the comorbid conditions associated with rhinitis, including nasal polyposis, acute and chronic rhinosinusitis, otitis media with effusion, obstructive sleep apnoea, and asthma.

Nasal polyposis

Nasal polyps are prolapses of the mucosa usually originating within the ethmoid sinus. They block the nasal airway so that the patient loses the sense of smell and taste. Polyps tend to cause rhinorrhoea, which usually appears as postnasal catarrh, and sometimes symptoms of rhinitis such as sneezing. Nasal polyps affect approximately 2% of the normal population, a similar proportion of individuals with allergic rhinitis, and around 5% of those with nonallergic rhinitis or atopic asthma. A much stronger association is seen with aspirin intolerance (36%), intrinsic asthma (13%), and cystic fibrosis (20%). The highest incidence of nasal polyps is among patients with Churg-Strauss syndrome (50%) (1).

This part of the paper is confined mainly to “allergic-type” polyps, so defined because although there is no association with IgE nor with a positive skin prick test, the histology is one of eosinophilia. Indeed the histologic changes include not only oedema and a thickened basement membrane but also an influx of inflammatory cells of all types – a histologic picture strongly reminiscent to that of asthma.

Management

The aims of management are either to reduce the size of, or to eliminate, the polyp(s). This relieves the rhinitis and the secondary symptoms of sinusitis and headache, restores smell and taste, and reduces the recurrence rate.

Surgical removal can be highly effective but is rarely curative; the recurrence rate is 80% within 73 months (2). Indeed, it is not unusual for patients to undergo multiple procedures to remove recurrent polyps.

The pathogenesis of eosinophil-dominated polyps is incompletely understood. There is, however, evidence of cytokine formation and release not only by T cells, mast cells, and stem cells, but also by the epithelium. There is reason to expect corticosteroids to interfere with this cytokine release and so prevent the subsequent trapping of myeloid precursors, and their development into mature cells such as eosinophils and basophils (Fig. 1). Certainly systemic steroids, especially the first course, can be extremely effective (3). However, their effects are poorly documented, and subsequent courses tend to have less effect (G. K. Scadding, personal observation). Furthermore, the significant side-effects of oral corticosteroids preclude their long-term use.

Topical corticosteroids

Topical corticosteroids have good anti-inflammatory activity, and there is evidence that many of them are effective in reducing the size of the polyp(s), the associated rhinitis symptoms (4–8), and, if used long-term, the likelihood of recurrence (9, 10).

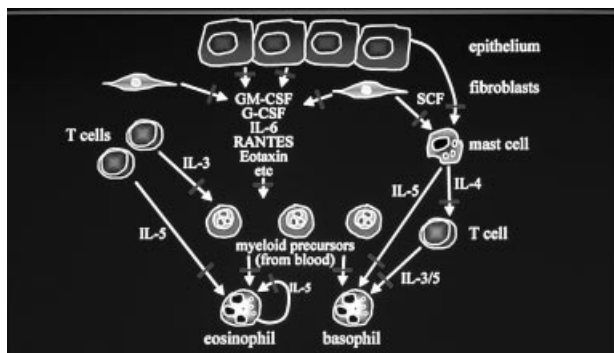


Figure 1. Sites of action of corticosteroids.

Fluticasone propionate (FP) has been shown to reduce polyp size in patients with mild and moderate rhinitis (4). In more severely affected patients, those receiving 3 months' treatment with FP were less likely to need surgery than those who received placebo (5).

Unfortunately, most polyps are beyond the easy reach of nasal sprays. Drops which can be used in the head-down-and-forward position, for example, betamethasone drops, are extremely effective, provided the patient remains in this position for a minute or so after application. Betamethasone drops, however, have systemic effects due to their virtually 100% bioavailability and lack of first-pass hepatic metabolism. They decrease morning cortisol levels, and reduce response to ACTH (11). Recently, Cushing's disease has been reported in three children receiving long-term treatment with betamethasone (12). Overdosing is common because the dose is not metered (13); hence, the need for an alternative.

FP drops were produced in response to this need. They have several important advantages over betamethasone drops (Table 1). Each dosing unit is used only once so the benzalkonium chloride preservative is not needed. The bioavailability of FP in this formulation is only 0.06%; i.e., less than that of the nasal spray (0.51%) (14). The low systemic bioavailability explains the lack of significant effect on cortisol levels observed in two 24-week trials (15, 16) – in marked contrast to the effects of betamethasone. The absence of preservative also reduces the risk of hypersensitivity reactions.

The efficacy of FP drops has been confirmed in two, randomized, double-blind, placebo-controlled, multi-centre trials (15, 16). In both studies, 12 weeks' randomized treatment was followed by 12 weeks' open-label therapy with the FP drops. Polyp size was

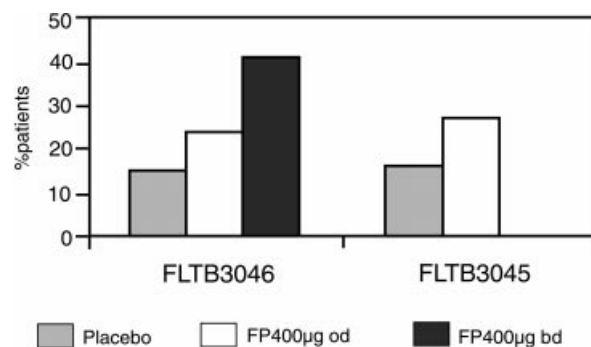


Figure 2. Efficacy of fluticasone propionate nasal drops (Keith et al. [15]; Penttila et al. [16]).

the primary end point, and was assessed endoscopically by a blinded observer; the secondary end point was nasal inspiratory peak-flow. Symptoms and olfaction were also recorded.

Reduction of polyp size with the FP drops was clearly dose-related, being greater with the 800 than the 400 µg dose (Fig. 2). Improvement in nasal inspiratory peak-flow was also somewhat greater with the higher dose, at least in the early weeks. All symptoms improved significantly at the higher dose, and only olfaction failed to improve with the lower one.

The drops were well-tolerated: the frequency and severity of most adverse effects was not significantly different from those seen with placebo. Only the incidence of minor epistaxis, 8–9%, was significantly higher in the FP than in the placebo group, and was similar to that seen with topical corticosteroid sprays.

Therefore, FP drops are the treatment of choice for mild to moderate allergic nasal polyps. The lower risk of systemic side-effects with FP than betamethasone enables treatment, if successful, to be continued long-term.

Asthma

It has been estimated that approximately 80% of asthmatics also suffer from rhinitis (17). Other studies have shown that rhinitis is a risk factor for the development of asthma (18). Histologically, the two disorders are very similar. Exacerbations of asthma are usually preceded by rhinitis, which is frequently viral. The effect of topical corticosteroids in reducing the expression of intercellular adhesion molecule-1 (ICAM-1), the rhinovirus receptor, may account for

Table 1. Advantages of FP compared with betamethasone drops

Fluticasone propionate drops	Betamethasone drops
Dosage control – no risk of patients taking more than prescribed dose	No dosage control – difficulty of using dropper results in patients taking up to 338% of prescribed dose
24-week trial – no significant effect on cortisol levels	6-week treatment – significant reduction in cortisol levels
Systemic bioavailability 0.06%	Systemic bioavailability unknown – thought to be 100%
Preservative-free – lack of hypersensitivity reactions	Occasional stinging/burning; smell?

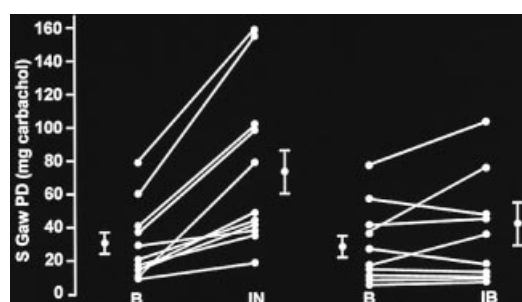


Figure 3. Different effects of nasal and bronchial corticosteroids (Aubier et al. [21]).

the improvement in asthma seen when the rhinitis is successfully treated. However, this is unlikely to be the mechanism in seasonal asthma where rhinitis treatment also leads to a reduction in chest symptoms (19). Topical corticosteroids used intranasally also reduce the bronchial hyperreactivity following allergen challenge (20). Indeed, there is evidence that intranasal beclomethasone 400 µg is more effective in reducing bronchial hyperreactivity than the same dose administered by inhalation (Fig. 3) (21).

The reasons for the benefit in asthma, of rhinitis therapy are uncertain. It may be relevant that rhinitis impairs the ability of the nose to warm, filter, and humidify inspired air. Other possible explanations lie in the nasobronchial reflexes or in the passage of cytokines, mediators, or infection from nose to chest. Possibly relevant is the fact that nitric oxide is present in bactericidal quantities (20–25 ppm) in the sinuses, to a lesser extent (500–800 ppb) in the nose, and in only small amounts (<10 ppb) in the chest.

Further research is needed; but, in the meantime, rhinosinusitis treatment is a sensible strategy in patients with poorly controlled asthma.

Chronic rhinosinusitis

The use of steroids to treat patients with chronic inflammation resulting from recurrent infection is controversial. The rationale is based on reducing both the inflammation, especially at the ostiomeatal complex where ventilation and drainage might be improved, and the immunologic over-reactivity. The risk of such treatment is that it may lead to secondary infection due to immune suppression.

Four studies have shown modest benefit of corticosteroids in chronic rhinosinusitis (22–25). Our own recent, double-blind, placebo-controlled study (26) of 200 µg FP bd. showed a trend for diary card symptoms to improve in both the FP and placebo groups, but there were no significant changes in the results of objective tests, such as acoustic rhinomanometry, endoscopy, or eosinophil count.

There was no evidence, however, that FP increased the number of acute bacterial infections.

Acute rhinosinusitis

A recent placebo-controlled study of FP 100 µg given within 48 hrs of onset and continued for 6 days showed a trend for a reduction in viral sinusitis at 1 week. In this double-blind, placebo-controlled study, sinus radiographs were performed at baseline, on day 7, and on day 21. Rhinosinusitis (defined by fluid level or >5 mm thickening) at day 7 was significantly more frequent in the placebo group (Table 2) (27).

Otitis media with effusion

This common condition of childhood is strongly associated with rhinitis. The explanation is uncertain. Abnormal Eustachian tube function, or up-regulation of ICAM-1 leading to increased frequency of viral infections, may be responsible.

The effect of rhinitis treatment is disputed. A meta-analysis of the effect of oral steroids shows a tendency for remission (28). There have been few trials of intranasal steroids, and none have been conclusive (29a, 29b). In our own open study, beclomethasone 100 µg a day halved the need for insertion or reinsertion of grommets and was associated with an overall improvement in the children's general health, including a 70% reduction in the frequency of colds, visits to the general practitioner, and the need for antibiotics (30). There were no significant growth problems associated with the use of this corticosteroid daily for over 1 year. A double-blind, placebo-controlled study of FPANS 100 µg daily is now in progress.

Allergic rhinitis in small children

This condition is difficult both to diagnose and treat. Very few drugs are available for children under 4 years of age. Sodium cromoglycate is effective if used regularly, but small children seldom comply with a nasal spray regimen requiring administration three or four times daily.

In a recent randomised, placebo-controlled, double-blind, double-dummy study (31), we compared

Table 2. Acute rhinosinusitis (Puhakka et al. [27])

	Acute rhinosinusitis		
	FP	Placebo	P
% Sinusitis day 7			
All subjects (n=169)	24.7	31	0.37
Rhinosinusitis-positive	18.4	34.9	0.07
% Sinusitis day 21			
All subjects (n=169)	8.2	7.1	0.79
Rhinosinusitis-positive	4.1	2.3	1.00

ketotifen 1 mg once daily and FPANS 100 µg daily in children with perennial rhinitis aged 2–4 years. FP was significantly more effective against night-time and daytime symptoms and nasal blockage. Nine of 13 children improved with FP, and 4/14 with ketotifen, and there were no drug-related adverse events.

Obstructive sleep apnoea

Approximately 80% of intranasal medication passes down the postnasal space, suggesting that this route might be used to reduce the size of pharyngeal lymphoid tissue such as adenoids. A small pilot study of FP suggested benefits in 4/6 children treated (32). Our own study of FP in children listed for tonsillectomy and adenoidectomy is in progress.

In a 4-week, double-blind, placebo-controlled study in 23 adult snorers who also suffered from nasal congestion, FP decreased the apnoea/hypopnoea index, nasal airway resistance, and nasal congestion, and increased daytime alertness. There was no evidence, however, that FP affected snoring (33).

Conclusion

The nose is the gateway to the respiratory tract and its associated organs, and many inflammatory conditions of the upper respiratory tract need effective treatment. This is now possible with the advent of very effective topical corticosteroids, such as fluticasone propionate, which can be safely used in low dosage for prolonged periods.

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