

## 5. Clinical performance of fluticasone propionate nasal drops

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The efficacy and safety of fluticasone propionate (FP) nasal drops were investigated in two multicentre, randomized, placebo-controlled trials. Patients received FP 400 µg once or twice daily for 12 weeks and then FP 400 µg once daily for a further 12 weeks. FP 400 µg significantly reduced polyp size and improved peak nasal inspiratory flow, rhinitis symptoms and sense of smell when administered twice daily. Significant reductions in polyp size were not achieved with once daily administration, but clinical benefits were observed for peak nasal inspiratory flow. Both dosing regimens were well tolerated, with an overall incidence of adverse events which was similar to placebo.

### Introduction

The changing treatment strategies over the last few decades have reduced the need for surgery in many cases of polyposis. Systemic corticosteroids have a very good effect as short-term treatment. Local corticosteroids are also effective in decreasing the size of polyps and the symptoms associated with polyposis (1), and, in some cases, abolishing polyps altogether. The results of two unpublished studies investigating fluticasone propionate (FP) nasal drops in patients with polyposis are presented here (2, 3).

### Efficacy of FP nasal spray

FP has been used worldwide as a nasal spray for several years. Studies in patients with allergic rhinitis have shown the nasal spray to be a very effective local treatment with low systemic bioavailability, comparing favourably with other corticosteroids such as beclomethasone dipropionate (4–7).

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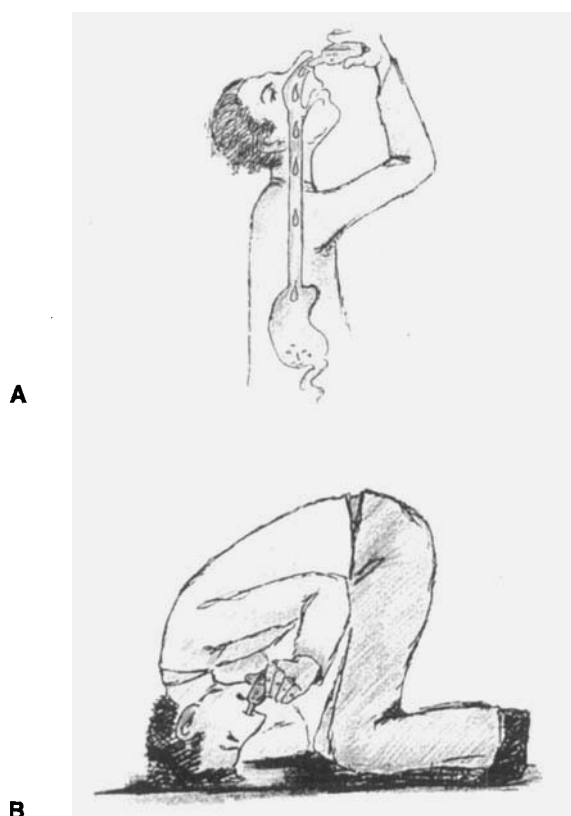


Figure 1. A) Administering drops in conventional position. B) Administering drops in head downwards and forwards position.

More recent studies in patients with nasal polyposis have shown that treatment with FP nasal spray can decrease the size of polyps and reduce the symptoms associated with polyposis (8–10). Objective measurements by an acoustic rhinometer have also shown an increase in nasal cavity volume after treatment with FP nasal spray (9).

## Improved efficacy with FP nasal drops

The efficacy of nasal corticosteroids in nasal polyposis may be improved by changing the formulation in order to increase the dose delivered to the middle and upper meatus, where the polyps originate (11). The administration position is also important in the delivery of FP nasal drops for polyposis. If the drops are administered in the conventional way, with the head tilted back, the drops will only reach the lower region of the nose and the stomach, and not the upper region where the polyps originate (Fig. 1a). To achieve complete delivery to the target area, the patient must use the “head downwards and forwards” position (Fig. 1b). An alternative position is to lie face down on the bed, with the head hanging over the side (12). It is best to

remain in these positions for a short time so the drops can reach the target site.

## Recent clinical studies of FP nasal drops

### Study design

Two multicentre, randomized, parallel studies have recently been conducted in patients with bilateral nasal polyposis to investigate the efficacy, dose-dependency and tolerability of FP 400 µg nasal drops administered once or twice daily (2, 3). All patients had mild (score 1) or moderate (score 2) polyps as assessed on the semiquantitative scale described by Johansen (13).

In both studies, the patients underwent the following trial periods: 2-week run-in, 12-week double-blind treatment, 12-week open treatment and 2-week follow-up (Fig. 2). In study 1, patients were randomized to receive either placebo ( $n=52$ ) or FP 400 µg once daily ( $n=52$ ). In study 2, patients were randomized to receive placebo ( $n=47$ ), FP 400 µg once daily ( $n=48$ ) or FP 400 µg twice daily ( $n=47$ ). In both studies, all patients received FP 400 µg once daily during the second 12-week treatment period.

### Measures of efficacy

The primary efficacy end point was polyp size. Polyp size was assessed by the investigators on a scale from 0 (none) to 3 (severe), depending on their position relative to the inferior turbinate (Fig. 3) (13). An improvement in polyp size required a change of at least one grade.

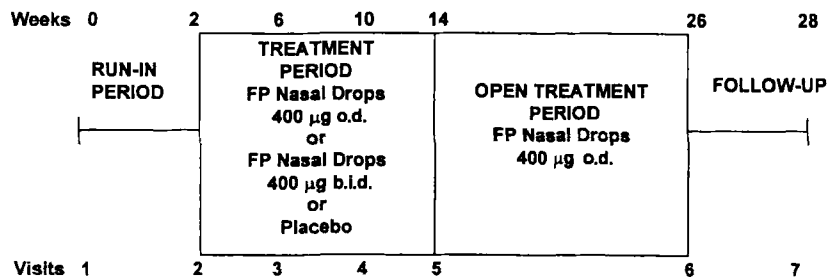
Secondary efficacy parameters included peak nasal inspiratory flow, symptom scores, olfactory function, use of rescue medication (loratadine) and the need for polypectomy. Peak nasal inspiratory flow was measured with a Youtlen meter (14). Polyposis symptoms such as nasal blockage, sense of smell, nasal discomfort and rhinitis were assessed on a scale from 0 (absent) to 3 (severe) by both patients and physicians. Olfactory function was assessed by a modified version of the University of Pennsylvania smell identification test (15) and the butanol threshold test (16).

### Results

In study 1, reductions in polyp size were observed in nearly 30% of FP recipients compared with 16% of placebo recipients; however, this difference did not reach statistical significance. A similar result was achieved in study 2 for

## Study Design Study 1/ Study 2

Figure 2. Schematic diagram of study design.



patients who received placebo or FP 400 µg once daily. However, significantly more recipients of FP 400 µg twice daily had a decrease in polyp size than recipients of placebo (41 % vs 15 %;  $P=0.006$ ). Although the difference between the two active treatment groups in study 2 was not statistically significant, the dose-dependent decrease of polyp size was still evident (Fig. 4).

Dose-dependent effects were also demonstrated with peak nasal inspiratory flow, the results of which are summarized in Table 1. The placebo groups in both studies showed little change in peak nasal inspiratory flow values, whereas recipients of FP 400 µg once daily had pronounced improvements. In study 2, patients who received FP 400 µg twice daily had greater improvements than those who received once-daily dosing.

The results for peak nasal inspiratory flow are consistent with relief of nasal blockage as assessed by both the patients and investigators. In study 2, both dosing regimens of FP showed significant improvements in nasal blockage, nasal discomfort and rhinitis symptoms compared with placebo (all  $P<0.05$ ). Use of rescue loratadine was minimal, with greater use in the placebo groups.

### Grading system for polyp assessment—coronal view of nose

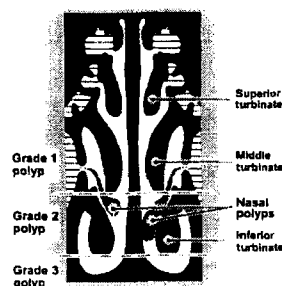


Figure 3. Polyp grading scale.

Although there were no significant differences between treatment groups in olfactory function, patients who received FP either once or twice daily tended to have greater improvements in olfactory function tests than placebo recipients.

### Adverse events

During the 12-week, double-blind treatment phase, a total of 100 patients received FP 400 µg once daily and 47 patients received FP 400 µg twice daily. After the initial 12-week treatment period, a total of 205 patients went on to receive FP 400 µg once daily in the open phase of the study.

An integrated summary of all the adverse events reported during this clinical programme is shown in Table 2. There were no differences between treatment groups in the overall frequency of adverse events, the number of treatment-related adverse events and the incidence of serious adverse events. No serious adverse event was considered by the investigators to be related to treatment.

### Percentage of patients showing an improvement in polyp size from baseline

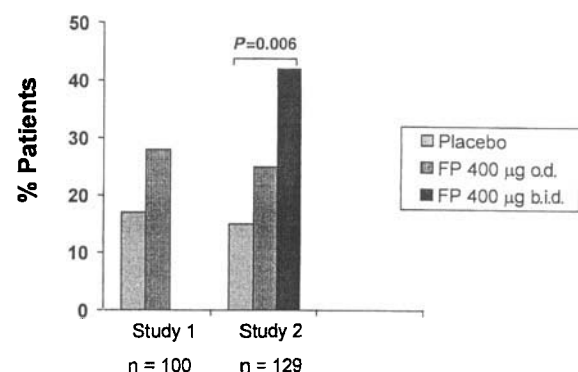


Figure 4. Polyp size data.

**Table 1.** Summary of changes in peak nasal inspiratory flow (weeks 1–12)

|                                 | Study 1 |                   | Study 2 |                   |                     |
|---------------------------------|---------|-------------------|---------|-------------------|---------------------|
|                                 | Placebo | FP 400<br>µg o.d. | Placebo | FP 400<br>µg o.d. | FP 400<br>µg b.i.d. |
| No. of patients                 | 49      | 51                | 38      | 46                | 43                  |
| Clinic PNIF <sup>1</sup>        | –3 (8)  | 52 (9)            | 3 (10)  | 24 (9)            | 48 (9)              |
| Diary card AM PNIF <sup>2</sup> | –2 (5)  | 45 (5)            | 0 (6)   | 22 (6)            | 35 (6)              |

<sup>1</sup>Adjusted mean change at end of treatment (se).  
<sup>2</sup>Mean change during treatment (se).

The most commonly reported adverse events were related to ear, nose and throat disorders. The incidence of adverse events such as throat irritation, nasal irritation, dryness of the nose and epistaxis, which are considered to be predictable for topical corticosteroid treatment, is summarized in Table 3. In study 1, the incidence of epistaxis was significantly higher in FP recipients than placebo recipients (19% vs 4%;  $P=0.028$ ). This may be a result of mild

**Table 2.** Integrated summary of adverse events reported during treatment period

|                                                         | Placebo  | FP 400 µg |          |             |
|---------------------------------------------------------|----------|-----------|----------|-------------|
|                                                         |          | o.d.      | b.i.d.   | o.d. (open) |
| No. of patients                                         | 99       | 100       | 47       | 205         |
| No. of patients (%) with any adverse event              | 59 (60%) | 47 (47%)  | 21 (45%) | 60 (29%)    |
| No. of patients (%) with any drug-related adverse event | 18 (18%) | 14 (14%)  | 5 (11%)  | 14 (7%)     |
| No. of patients (%) with serious adverse event          | 1 (1%)   | 1 (1%)    | 0        | 2 (<1%)     |
| No. of patients (%)                                     | 9 (9%)   | 1 (1%)    | 2 (4%)   | 0           |

**Table 3.** Summary of predictable adverse events

|                                             | Study 2  |                   |                     | Study 1  |                   | Study 1/<br>Study 2         |
|---------------------------------------------|----------|-------------------|---------------------|----------|-------------------|-----------------------------|
|                                             | Placebo  | FP 400<br>µg o.d. | FP 400<br>µg b.i.d. | Placebo  | FP 400<br>µg o.d. | FP 400<br>µg o.d.<br>(open) |
| No. of patients                             | 47       | 48                | 47                  | 52       | 52                | 205                         |
| No. of patients with any adverse events     | 27 (57%) | 16 (33%)          | 21 (45%)            | 32 (62%) | 31 (60%)          | 127 (62%)                   |
| No. of patients with any predictable events |          |                   |                     |          |                   |                             |
| Throat irritation                           | 1 (2%)   | 0                 | 0                   | 3 (6%)   | 2 (4%)            | 3 (1.5%)                    |
| Nasal irritation                            | 0        | 1 (2%)            | 0                   | 1 (2%)   | 0                 | 2 (1%)                      |
| Dryness of nose                             | 0        | 0                 | 0                   | 0        | 1 (2%)            | 0                           |
| Epistaxis                                   | 1 (2%)   | 4 (8%)            | 4 (9%)              | 2 (4%)   | 10 (19%)          | 6 (3%)                      |

nosebleeds being included in the definition of epistaxis. One patient who received FP 400 µg twice daily was withdrawn because of intermittent epistaxis. This profile is in line with the increased risk of nosebleed known to be associated with intranasal corticosteroids [17, 18].

Routine laboratory tests on urine and blood samples showed no effects of treatment in any patient group, and there were no significant changes in morning serum cortisol levels collected before and after treatment. This was not unexpected, as the systemic bioavailability of FP nasal drops is even lower than with the nasal spray (0.06% vs 0.5%) [6, 7].

## Conclusions

These two clinical studies have demonstrated that both dosing regimens of FP nasal drops reduced polyp size compared with placebo, with a significantly greater reduction resulting from twice-daily dosing than a once-daily

regimen. Similarly, both dosing regimens of FP nasal drops improved peak nasal inspiratory flow and symptoms of polyposis and rhinitis. FP nasal drops were well tolerated

and had no significant effect on mean serum cortisol levels. Thus, FP nasal drops are an effective, safe and convenient treatment option for nasal polyposis.

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