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Prophylactive treatment with flunisolide after polypectomy

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SUMMARY

Twenty-two patients with nasal polyps completed a double-blind study with a new topical corticosteroid, flunisolide. Treatment during three months after operation gave, in comparison with placebo, a statistically significant effect on the symptom of stuffy nose, and on the sum of scores for stuffy nose, runny nose and sneezing. There was no significant effect on rhinomanometry. Side effects were negligible. Three patients in the placebo-group required a further operation within one year but none in the flunisolide group. Prophylactic treatment with flunisolide can be recommended as a complement to other treatment after surgery of nasal polyps.

INTRODUCTION

The aetiology of nasal polyps is still obscure. An allergic aetiology is often presumed but in only some cases are nasal polyps combined with allergic diseases (Caplin et al., 1971). Aspirin intolerance is an established factor in nasal polyposis, as it is for asthma (Holopainen et al., 1979). A few cases of nasal polyps occur in mucoviscoidosis (Schwochmann et al., 1961) and Kartagener's syndrome. According to studies performed by Mygind (1978), most polyps are of infectious origin.

Since our knowledge of the aetiology and pathogenesis of nasal polyps is weak, any treatment must therefore be regarded as purely symptomatic.

Topical Corticosteroids

On the basis of the theory that the pathogenesis of nasal polyps includes components of inflammatory and/or allergic reaction, topical steroids have been used for more than a decade. Topical Beclomethazone dipropionate (Bdp) has been used for the treatment of nasal polyps, as well as for perennial and vasomotor rhinitis and, in doses of 400 µg per day, no systemic reactions or changes in plasma cortisol levels have been observed (Mygind, 1978).

Mygind et al. (1975) reported good results in a double-blind investigation using Bdp during 3 weeks in 35 patients with nasal polyps. Daily scores of sneezing, nasal secretion and nasal blockage were found to decrease considerably in comparison with the placebo-group. This group of patients had been operated on for

an average of 8 times before the investigation. A double-blind cross-over investigation in patients with nasal polyps (Deuschl and Drettner, 1977) using Bdp topically in doses of 400 µg per day gave good results, especially for nasal blockage, rhinomanometry showing that nasal patency improved significantly during the treatment period. However, the polyps did not disappear during such a 4-week period.

Long-term topical treatment of nasal polyps with Bdp (Pedersen et al., 1976) was evaluated over one year and showed good results in 80% of the patients but some with large polyps required surgery.
Virolainen et al. (1980) performed a double-blind investigation where they studied the effect of Bdp in a daily dose of 400 µg during one year after radical ethmoidectomy for nasal polyps in 46 patients. They found a statistically significant effect in the actively treated group on subjective nasal symptoms, recurrencies of nasal polyps and nasal patency which was estimated by rhinomanometry.
Klemi et al., (1980) investigated nasal biopsy in their patients after one year's treatment and did not find any sign of atrophy or other effects which could be attributed to the treatment.

Flunisolide
Topical Bdp has opened a way for the treatment of various nasal diseases but the results have been less favourable for nasal polyps than for perennial and vasomotor rhinitis. Several other steroids have since been manufactured, which are also suitable for nasal application (Balle et al., 1980). Flunisolide is such a steroid, which has already been tested in perennial and seasonal allergic rhinitis (Backhouse, 1979; Bloom et al., 1977, Incaudo et al., 1980; Saito, 1981). Flunisolide is prepared as an aqueous solution of 0.025% concentration with a mixture of propylene glycol and polyetylenglycol as vehicle. A daily dose of 200 µg, divided into 2 administrations a day, is usually used. The pump delivery system, which gives 25 µg of flunisolide per spray, does not, in contrast to becotide (Bdp), include any aerosol propellants, which is an advantage since these sometimes cause local burning and irritation. The droplets produced by the device are in excess of 11 µm which is a size where almost all particles are deposited in the nose, and almost no penetration to the lower airways occurs. A dose of 200 µg flunisolide per day has no demonstrable effect on plasma cortisol levels and the safety margin, in respect of systemic side effects, has been reported to be wide (Schulz et al., 1978; Pakes et al., 1980; Sahay et al., 1980; Clayton et al., 1981).
Beneficial effects of topical flunisolide have been reported in a long-term study of 339 patients with perennial rhinitis, of whom 52 were followed more than one year (Crepea, 1978). Other reports, using placebo controls, have demonstrated favourable effects in hay fever and perennial rhinitis (Bloom et al., 1977; Sahay et

al., 1979; Clayton et al., 1981). A few well-designed comparative studies have shown 200 µg flunisolide per day to be as effective as intranasal Bdp 400 µg per day in perennial rhinitis (McAllen et al., 1980; Pakes et al., 1980; Sahay et al., 1980).

Side effects, consisting of mild burning and stinging of brief duration and episodes of epistaxis, have been reported with about the same frequency as with Bdp (McAllen et al., 1980; Sahay et al., 1980).

The local effect on the nasal mucosa has been studied by taking biopsies before and after treatment with 200 µg per day during 3 months for allergic perennial rhinitis (Sahay et al., 1980). No significant effect on the surface epithelium of the nasal mucosa was found.

Purpose of the investigation

No investigation into the effect of topical flunisolide on nasal polyps has appeared in the literature. As the published results on the use of Bdp in nasal polyps indicate that surgery cannot be avoided with topical steroids, it was decided to perform a double-blind study in patients who had recently undergone operation for nasal polyps. The aim of the investigation was thus to study the possible preventive effect of flunisolide on the recurrent polyps after surgery.

MATERIAL AND METHODS

Candidates for the study were selected from patients in whom surgery of nasal polyps had been undertaken on one or more occasions. The patients were randomised and the code was not broken until the study was completed.

Conditions which excluded patients from the study were:

1. Previous surgery of the septum or radical surgery of the maxillary sinus.
2. Recurrent epistaxis.
3. Pregnancy.
4. Allergy to steroids.
5. Treatment with corticosteroids systemically or topically during the 3 months prior to the study.
6. Unstable treatment regimens for asthma or allergic rhinitis.
7. Acute psychosis, active peptic ulcer, tuberculosis, ocular herpes simplex, chickenpox, or any major uncontrolled illness.
8. Fungal or other clinically apparent nasal infection or atrophic rhinitis.

The series consisted of 25 consecutive patients (19 men and 6 women) fullfilling the criteria mentioned previously. The mean age in the flunisolide group was 46 years and in the placebo-group 41 years. Only one previous polypectomy had been performed in 11 patients and two or more in the other 14. For personal

reasons, 3 patients with active treatment dropped out before the study was finished. The final number completing the treatment thus consisted of 11 patients with active treatment and 11 with placebo. The estimated duration of polyposis was 11 years in the flunisolide group and 18 years in the placebo-group; this difference being non-significant. There were no differences between the active and the placebo-group in respect of their previous relevant disease histories (Table 1).

Table 1. Case histories.

	flunisolide	placebo
perennial rhinitis	3/11	4/11
seasonal rhinitis	2/11	2/11
seasonal asthma	1/11	0/11
asthma	1/11	1/11
hypersensitivity	3/11	4/11
chronic sinusitis	1/11	3/11
heredity for allergy	2/11	4/11
desensitization performed	0/11	1/11

The patients were asked about their intake of other medicines; sporadic use of acetylsalicylic acid was reported by 10/22. Cortisone therapy had been given to 4/22, more than 3 months prior to the study. Antihistamines were used by 3 patients and one used Salbutamol. There was no significant difference between the two groups in respect of medication.
The mean time since last operation was 7.4 years for the flunisolide group and 3.8 years in the placebo-group but this was not a significant difference. The mean number of earlier polypectomies was 5.4 in the flunisolide group and 6.7 in the placebo-group; neither was this significant.

Active treatment with 0.025% flunisolide nasal spray was given with 2 sprays to each nostril twice a day to a total daily dose of 200 µg. The placebo treatment consisted of the vehicle propylene glycol and polyetylenglycol in the same concentration as in the flunisolide solution and was given exactly in the same way as the active treatment. The duration of the treatment was 3 months, beginning 4 weeks after surgery, which was, in all cases a complete as possible removal of the polyps.

All the patients reported their weekly symptoms of nasal blockage, sneezing and nasal secretion on a diary card according to a score: none (0), mild (1), moderate (2) and severe (3). The patients were examined before surgery and 1, 2, 3 and 4 months after. Each examination included anterior and posterior rhinoscopy with estimation of the size of the polyps in none (0), small (1), medium (2) and large (3). Furthermore, nasal obstruction, nasal secretion and state of nasal mucosa were

scored separately. Side effects were elicited by general questioning. Any concomitant medication was also recorded. Rhinomanometry was performed prior to treatment and after 3 months treatment. The results were expressed as the nasal airflow at a differential pressure of 10 mm water between the nasopharynx and the nostrils. Only the results of posterior rhinomanometry of the total passage were evaluated. Ophtalmologic examination was performed with a slit lamp and tonometry on all patients except one, before and after treatment.
Nasal secretion was cultured for bacteria and fungi before nasal topical treatment, and after 3 months.
The statistical evaluation was done with t-test and Mann-Whitney's u-test.

RESULTS

When the relative effects of flunisolide and placebo were evaluated, the monthly results for the symptoms of "stuffy nose" alone (Fig. 1) and the combined scores for stuffy nose, runny nose and sneezing (Fig. 2) were significantly better for each of the three months with the active therapy ($p < 0.05$ for both differences).
Three patients belonging to the placebo-group had to be operated on once again, in less than one year, because of recurrence of polyps while none in the active group required a further operation within one year. Two of these patients had not previously been operated upon for nasal polyps, while one had undergone three earlier operations.

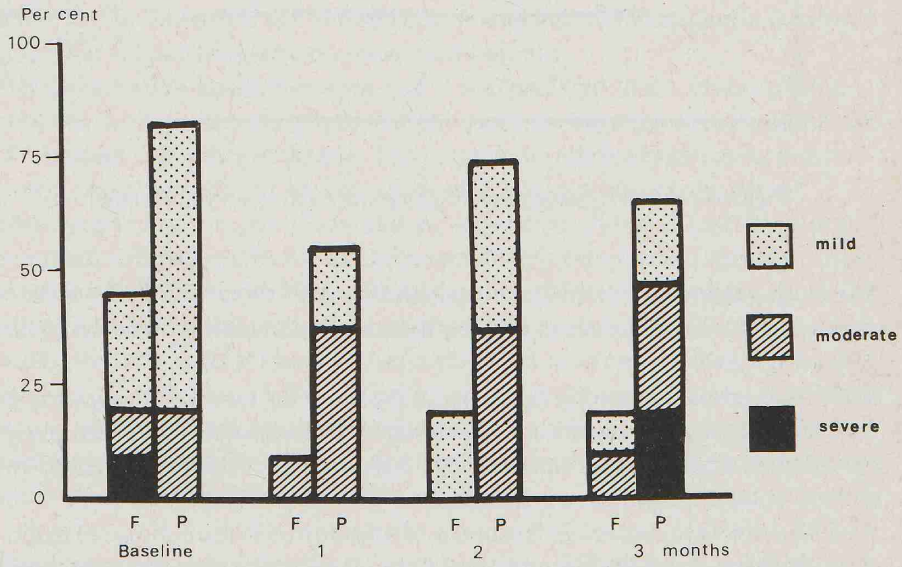

Figure 1. The result of the doctor's monthly interview concerning stuffy nose in flunisolide (F) and placebo (P) group.

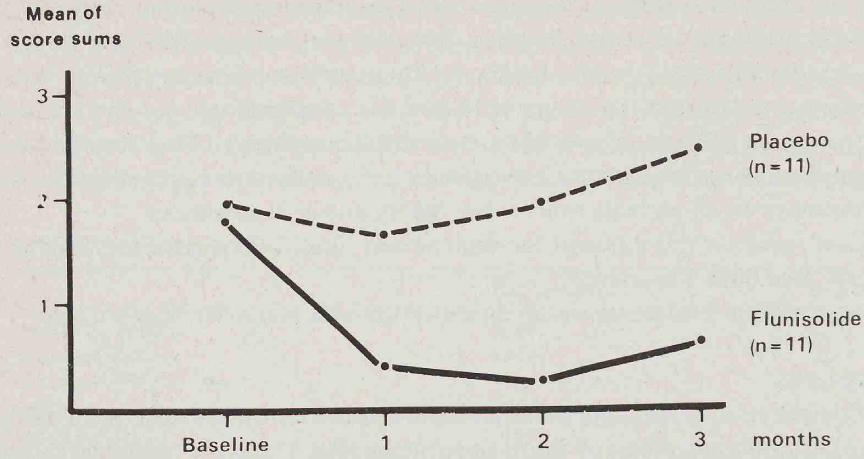

Figure 2. The mean of score sums for stuffy nose, runny nose and sneezing achieved by the doctors interview of the patients.

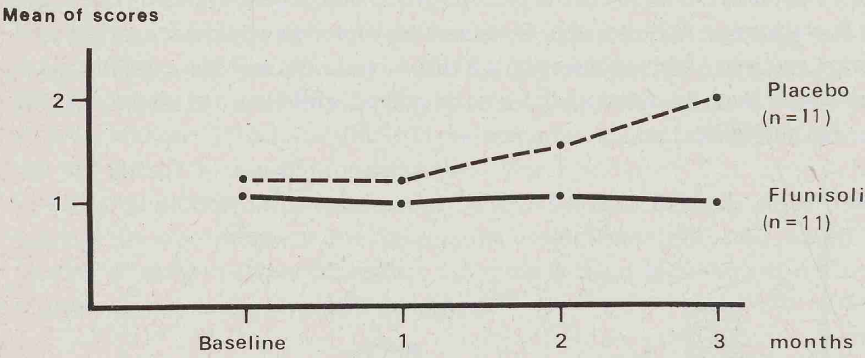

Figure 3. Monthly estimation of pólyp size by anterior rhinoscopy.

There was a tendency, although not statistically significant, to a smaller score of rhinoscopically estimated polyp size after three months treatment in the flunisolide group (Fig. 3).

Stuffy nose, evaluated weekly by the patients, showed a tendency to increase in the placebo-group but was constant and lower in the flunisolide group though not significantly. There was no demonstrable difference in the effect of therapy on primary polyps, as compared with recurrent polyps.

No difference was observed in frequency of infection or in the cultures of pathogenic bacteria. There was no growth of fungi. Rhinoscopy showed no mucosal atrophy. The nasal patency measure by rhinomanometry showed no difference between the two groups. Ophtalmologic examination showed one case with bi-

lateral cataract in the active group. This patient unfortunately was the only one not investigated before the treatment.
Generally, the patients accepted the treatment well. The number of side effects reported is shown in Table 2. There was no difference between active treatment and placebo.

Table 2. Side effects.

	flunisolide	placebo
temporary nasal irritation after spraying	1/11	7/11
blood stained mucus	3/11	-
nasal crusts	1/11	-
runny nose	-	1/11
sneezing	-	-
irritation in pharynx	-	1/11
irritation in the eyes	1/11	-
cataract	1/11	-
number of patients with side effects	4/11	7/11

DISCUSSION

There was no statistical difference in the two groups before the treatment. The beneficial effect of flunisolide was demonstrated as statistically better subjective scores, particularly in relation to stuffy nose. Furthermore, 3 cases required a repeat operation within one year in the placebo-group, compared with none in the active group. The polyp size showed only a tendency to be smaller in the active group but rhinomanometry revealed no difference.
The investigation lasted 3 months and it is considered that a longer treatment would be desirable but the duration of the trial was restricted because of the risk of drop-outs increasing with time. The therapeutic effect of preventing polyp regrowth can obviously not be evaluated until after a relative long period.
Rhinomanometry, in this investigation. showed no difference between active treatment and placebo. However, rhinomanometry does not detect small changes (Kumlien and Schiratzki, 1978; Hasegawa et al., 1979). Furthermore, since the polyps were removed before the medical treatment started, no immediate effect on the size of the polyps could be expected, and recurrencies may appear only later. In a previous study on patients with polyps prior to surgery who were treated with local Bdp and placebo, in a cross-over investigation, it was found that local Bdp had a positive effect on nasal patency, as demonstrate by rhinomanometry (Deuschl and Drettner, 1977).

There were few local side effects, and no difference in major side effects were noted between active treatment and placebo. Only one patient noticed irritation after the flunisolide spray. However, 7 of the patients in the placebo-group, using

exactly the same vehicle, noticed irritation; no reasonable explanation for this difference can be offered.

One patient treated with flunisolide required an operation for removal of a cataract one year after the treatment. A possible drug-related effect was seriously considered (Hill, 1978). However, it seems improbable that the cataract was an effect of the treatment because the patient had subjective symptoms with blurred vision before starting the treatment. In an investigation where 339 patients were treated in a long-term study with flunisolide, and 91 ophtalmological examinations were performed after 6 to 18 months treatment, no signs of cataract or glaucoma were found (Crepea, 1978).

CONCLUSIONS

Twenty-five patients with nasal polyps were treated with flunisolide nasal spray or placebo, in a double-blind study of 3 months duration starting one month after polypectomy. The patients included in the study had undergone operation on one or more occasions. Twenty-two patients completed the study and both the active and the placebo-group consisted finally of 11 patients.

Statistically significant effects on stuffy nose and on the total score of stuffy nose, runny nose and sneezing were found. No patients in the active group required a further operation for polyps during an observation time of one year, while 3 patients in the placebo-group had to be operated upon within one year. Only a few local side effects were reported with no difference in the incidence between the groups.

Prophylactic treatment with flunisolide nasal spray can be used as an adjuvant to the surgical treatment of nasal polyps. However, a long-term study will be necessary before a more definitive evaluation of the possible benefits of this therapy in the prevention of recurrence of polyps can be determined.

ZUSAMMENFASSUNG

An 22 Patienten mit Nasenpolypen wurde eine Doppel-Blind-Studie mit einem neuen Corticosteroid - Flunisolide - Präparat ausgeführt. Die Behandlung während 3 Monaten nach der Operation gab, im Verhältnis zum Placebo, einen statistisch bestätigten Effekt auf Beschwerden mit verstopfter Nase und auf die Summe der Schätzung von Beschwerden mit verstopfter und laufender Nase sowie Niesen.

Rhinomanometrimessungen gaben keinen signifikanten Unterschied. Die Nebeneffekte waren ohne Bedeutung. Drei Patienten in der Placebogruppe wurden innerhalb eines Jahres reoperiert, aber keiner von der Gruppe, die mit aktiver Substanz behandelt worden war.

Prophylaktische Behandlung mit Flunisolide kann als Komplement anderer Behandlungen nach der Operation von Nasenpolypen empfohlen werden.

REFERENCES

1. Backhouse, C. I., 1979: Intra-nasal flunisolide in the treatment of allergic rhinitis in general practice. Current Medical Research Opinion 6, 14–19.
2. Balle, V. H., Pedersen, U. and Engby, B., 1980: Allergic perennial and non-allergic vasomotor rhinitis treated with budesonide nasal spray. Rhinology 18, 135–142.
3. Bloom, F. L., Cohan, R. H., Leifer, K. N., Spangler, D. L., Rhoades, R. B. and Wittig, H. J., 1977: Flunisolide aerosol in the treatment of perennial allergic rhinitis. Ann. Allergy 38, 408–412.
4. Caplin, I., Haynes, J. T. and Spahn, J., 1971: Are nasal polyps an allergic phenomenon? Ann. Allergy 29, 631–634.
5. Clayton, D. E., Kooistra, J. B., Geller, M., Ouellette, J., Cohen, M., Reed, C. E. and Busse, W., 1981: Short-term efficacy trial and twenty-four-month follow-up of flunisolide nasal spray in the treatment of perennial rhinitis. J. Allergy Clin. Immunol. 67, 2–7.
6. Crepea, S., 1978: Flunisolide nasal spray perennial rhinitis long-term open study. Syntex Corporation, Memorandum, March 21.
7. Deuschl, H. and Drettner, B., 1977: Nasal polyps treated by beclomethasone nasal aerosol. Rhinology 15, 17–23.
8. Hasegawa, M., Kern, E. B. and O'Brien, P. C., 1979: Dynamic changes of nasal resistance. Ann. Otol. Rhinol. Laryngol. 88, 66–71.
9. Hill, R., 1978: Nasal insufflation study with an RS 3999 (flunisolide) formulation using rabbits (one year study). Syntex Research, Memorandum, February 20.
10. Holopainen, E., Mäkinen, J., Paavolainen, M., Palva, T. and Salo, O. P., 1979: Nasal polyposis. Acta Otolaryngol. 87, 330–334.
11. Incaudo, G., Schatz, M., Yamamoto, F., Mellon, M., Crepea, S. and Johnson, J. D., 1980: Intranasal flunisolide in the treatment of perennial rhinitis: Correlation with immunologic parameters. J. Allergy Clin. Immunol. 65, 41–49.
12. Klemi, P. J., Virolainen, E. and Puhakka, H., 1980: The effect of intranasal beclomethasone dipropionate on the nasal mucosa. Rhinology 18, 19–24.
13. Kumlien, J. and Schiratzki, H., 1978: Methodological aspects of rhinomanometry. Rhinology 17, 107–114.
14. McAllen, M. K., Portillo, P. R., Parr, E. J., Seaton, A. and Engler, C., 1980: Intranasal flunisolide placebo and beclomethasone dipropionate in perennial rinitis. Br. J. Chest Dis. 74, 32–36.
15. Mygind, N., Pedersen, C. B., Prytz, S. and Sørensen, H., 1975: Treatment of nasal polyps with beclomethasone dipropionate aerosol. Clin. Allergy 5, 159–164.
16. Mygind, N., 1978: Nasal allergy. Blackwell Scientific Publications (Oxford).
17. Pakes, G. E., Brogden, R. N., Heel, R. C., Speight, T. M. and Avery, G. S., 1980: Flunisolide: A review of its pharmacological properties and therapeutic efficacy in rhinitis. Drugs 19, 397–411.
18. Pedersen, C. B., Mygind, N., Sørensen, H. and Prytz, S., 1976: Long-term treatment of nasal polyps with beclomethasone dipropionate aerosol. Acta Otolaryngol. 82, 256–259.
19. Sahay, J. N., Ibrahim, N. B. N., Chatterjee, S. S., Nassar, W. Y., Lodge, K. V. and Jones, C. W., 1979: Long-term study of flunisolide treatment in perennial rhinitis with special reference to nasal mucosal histology and morphology. Clin. Allergy 10, 451–457.
20. Sahay, J. N., Chatterjee, S. S. and Engler, C., 1980: A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin. Allergy 10, 65–70.
21. Saito, Y., 1981: Treatment of perennial and seasonal allergic rhinitis with flunisolide nasal spray: An open trial and a multi-centre double-blind trial. Rhinology Suppl. 1, 215–218.

22. Schulz, J. I., Johnson, J. D. and Freedman, S. O., 1978: Double-blind trial comparing flunisolide and placebo for the treatment of perennial rhinitis. Clin. Allergy 1, 313–320.
23. Schwochmann, H., Kylezycid, L. L. and Mueller, H. D., 1961: Nasal polyposis in patients with cystic fibrosis. Am. J. Dis. of Children 102, 768–769.
24. Virolainen, E. and Puhakka, H., 1980: The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. Rhinology 18, 9–18.

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