Intranasal steroids and septum perforation – an overlooked complication? A description of the course of events and a discussion of the causes*

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SUMMARY

The use of intranasal steroids for the treatment of allergic and vasomotor rhinitis has doubled during the past 5 years. The number of reported cases of nasal septum perforation has increased correspondingly. The mechanism behind this is unknown, and steroid-induced septum perforation is rarely described in the literature. In order to describe the course of events and to form an idea of the extent of the problem, we have reviewed the cases reported at our clinic and compiled reports on side-effects from the Swedish Medical Products Agency.

In our department we found 32 patients with septum perforation (21 women and 11 men). The most common risk factor for septum perforation was steroid treatment, 11 cases (10 women, 1 man, average age 33 years, range 19-49 years). The information obtained from the Swedish Medical Products Agency showed that 38 cases of steroid induced septum perforation had been reported during the past 10 years. The number of side-effects per million Defined Daily Dose (DDD) was averaged to 0.21. The risk of perforation is greatest during the first 12 months of treatment and the majority of cases involves young women. We conclude that septum perforation due to nasal sprays are underreported in Sweden and that perforations are most likely to appear in young females during their first months of medication.

Key words: nasal septum, topical steroids, perforation

INTRODUCTION

Doubled use

Allergic rhinitis and other hypersensitive reactions in the upper airways appear to be increasing in frequency. Intranasal steroids have been in use since the 70s and provide effective and reliable treatment of allergic and vasomotor rhinitis. A few case reports of nasal septum perforation associated with the use of nasal steroids have been published (Schoelzel et al., 1985; Soderberg-Warner, 1984).

In Sweden, the number of reported side-effects in the form of septum perforation following the use of nasal steroids has increased from 1 to 2 cases per year, in the middle of the 80s, to 10 cases in 1995. This increase probably reflects the increase in the use of intranasal steroids.

In the Lund medical care district, the amount of nasal steroids delivered to pharmacies doubled between 1990 and 1955 (from 10.8 DDD/1000 inhabitants/day to 19.6 DDD/1000 inhabitants/day (DDD= Defined Daily Dose).

We have also observed a number of cases of septum perforation in which a connection is suspected with local steroid treatment. To investigate a possible link between septum perforation and the use of intranasal steroid sprays, we have retrospectively reviewed our records of septum perforation and compared them with the Swedish Medical Products Agency's reports on side-effects.

METHOD

Clinical cases and the Swedish Medical Products Agency's statistics

The diagnosis of all out-patients attending the Department of Oto-Rhino-Laryngology in Lund has been recorded since 15 July 1993. All patients given the diagnosis septum perforation (WHO code ICD-9, 478B) between 15 July 1993 and 30 September 1995 were identified from the patient database. In order to elucidate possible risk factors, the patient records were examined according to a specially designed template. Complementary information was obtained through a questionnaire which was sent to all iden-

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tified patients, and where necessary, patients were contacted by telephone. The risk factors we wished to elucidate were: use of intranasal cortisone spray or powder, decongestant nose-drops, allergy, smoking, previous nasal trauma, previous nasal surgery, excessive nose-picking behaviour and repeated cauterization for nosebleeds.

Case descriptions from all reports of nasal septum perforation and nasal steroids (1985 - 15 October 1995) were obtained from the Swedish Medical Products Agency.

RESULTS

Steroid-induced perforation occurs early

The Lund medical care district has a population of about 180,000, and about 28,000 appointments are made at the Department of Oto-Rhino-Laryngology each year. We found 32 patients in our database with septum perforation (21 women and 11 men). The average age of the whole group at the time of diagnosis was 39 years (range 10-75 years).

The material consists of cases which have accumulated during a long period, but which have been current at the Department since 15 July 1993. The number of new cases in 1993 was 6, in 1995, 4 and in 1995, until 30 September, 1. The most common risk factor for septum perforation was steroid treatment, 11 cases (10 women, 1 man, average age 33 years, range 19-49 years). Indications for treatment were: allergic rhinitis, 4 cases; idiopathic (vasomotor) rhinitis, 4 cases and chronic rhinitis, 3 cases. Among other possible causes were: previous septoplasty, 7 cases; long-term use of vasoconstrictive nose-drops, 6 cases (5 of which had also used nasal steroids); excessive nose-picking, 4 cases, and repeated cauterisation with chromium oxide for nosebleeds, 4 cases. One of the patients had worked in the galvanising industry (handling chromium and sulphuric acid) and one patient had systemic vasculitis. Four of the 11 who had used nasal steroids suffered nosebleeds before the septum perforation was discovered, and all suffered from crusting in the nose.

Table 1 Number of patients diagnosed as having septum perforation during treatment with nasal steroids. The material is from the Swedish Medical Products Agency and the Department of Oto-Rhino-Laryngology, University Hospital, Lund University.

Length of treatment (Months)	Swedish Medical Products Agency	Dept. of Oto-Rhino-Laryngology, Lund
0-6	12	3
7-12	8	5
13-18	4	1
19-24	0	1
25-30	2	1
31-36	1	0
>36	7	0

The information obtained from the Swedish Medical Products Agency showed that 38 cases of nasal septum perforation due to topical steroids had been reported during the past 10 years, 23 Rhinocort Aqua™ (budesonide in aqueous spray solution containing potassium sorbate as preservative, Astra-Draco, Sweden), 9 Rhinocort turbuhaler™ (budesonide as a dry powder without preservatives, Astra-Draco, Sweden), 5 Becotide nasal™ (beclomethasone in aqueous spray solution containing benzalconium chloride as preservative, Glaxo Wellcome, UK) 1 Flutide nasal™, (fluticasone in aqueous spray solution containing benzalconium chloride as preservative, Glaxo Wellcome, UK). The number of side-effects per million DDD were 0.19, 0.25, 0.13 and 0.29 for each pharmaceutical.

The distribution according to sex showed, as for our combined material, a higher tendency for women (73%, n=49) than for men (Fig. 1). Over half of the patients (28 of 45 evaluated) suffered septum perforation within a year of commencing steroid treatment (Table 1).

CASE REPORT 1

A 34-year-old women had perennial allergic rhinitis and asthma. She was being treated with budesonide and salbutamol for the lower airways and occasionally vasoconstrictive nosedrops at night. In January 1994, she was prescribed a nasal dry powder, budesonide (Rhinocort turbuhaler™). After 6 weeks at a return visit to the department she complained of nasal crusting and epistaxis. Nasal examination revealed crusting and irritated mucosa. Three weeks after the cessation of budesonide medication the mucosa had healed. She was then prescribed beclomethason nasal spray (Becotide nasal™) with careful instructions to aim the spray laterally in the nose. On a return visit, 3 weeks later, physical examination revealed an irritated and very thin mucosa and the septal cartilage was exposed over an area of about 2 × 2 mm. Beclomethason medication was replaced by an H_1-antagonist spray, levocabastine (Tilavist™). At the next return visit, 3 months later, the septum mucosa had healed leaving scarring of the mucosa.

CASE REPORT 2

A 27-year-old female was prescribed nasal dry powder, budesonide (Rhinocort turbuhaler™) due to sinusitis. After about 3 weeks of medication she had problems due to crusting and haemorrhage. In spite of her symptoms, she continued with her medication and sought advice 2 months later. She had then developed a large septal perforation of about 15 mm in diameter. The mucosa was highly inflammed with crusting and bleeding and a tentative diagnosis of Wegeners Granulomatosis was made. Extensive workup was, however, negative. After 8 weeks without medication her mucosa had completely healed, with no signs of inflammation. Her septum perforation remains. She has since then been without medication and she has been followed up for 2 years without any signs of mucosal inflammation.

Comments to case reports

Both these case reports show that a septum perforation may develop within weeks of the start of medication. Crusting and

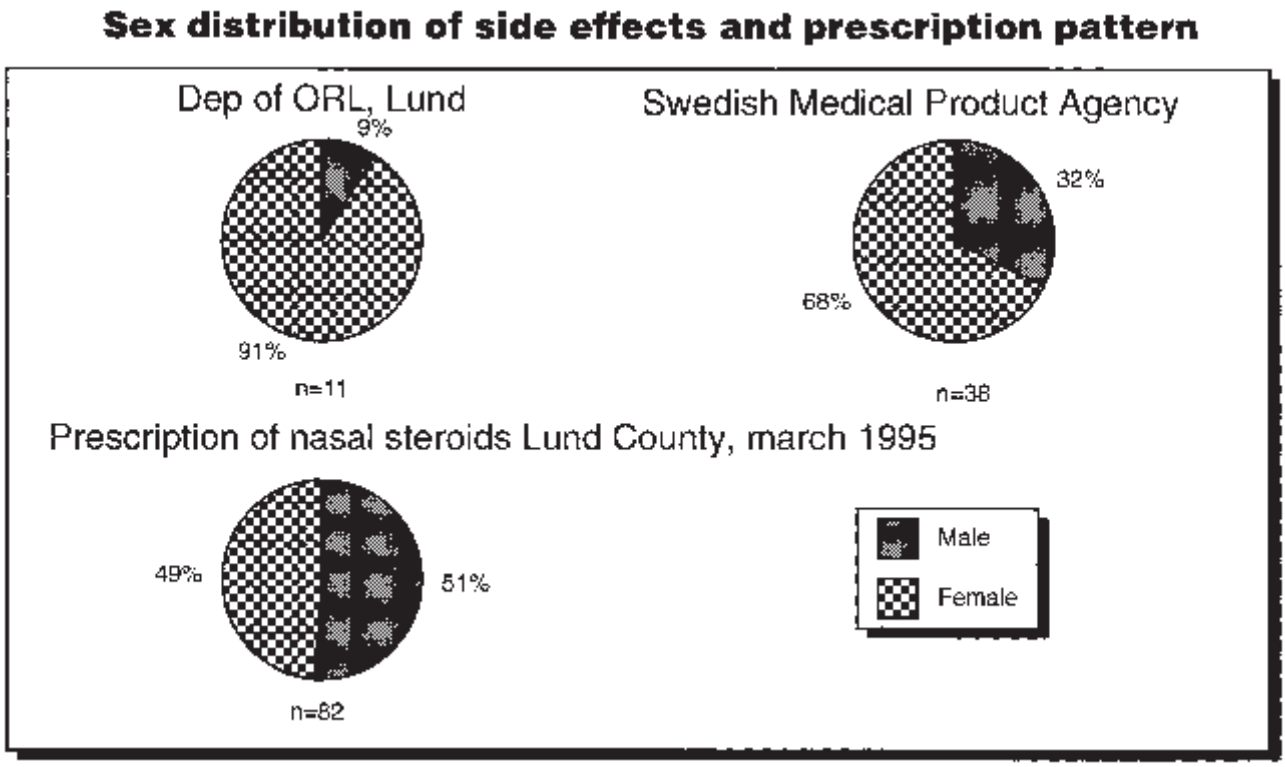

Figure 1. More women than men are affected by septum perforation after having used nasal steroids. This pattern is not reflected in the population prescribed nasal steroids.

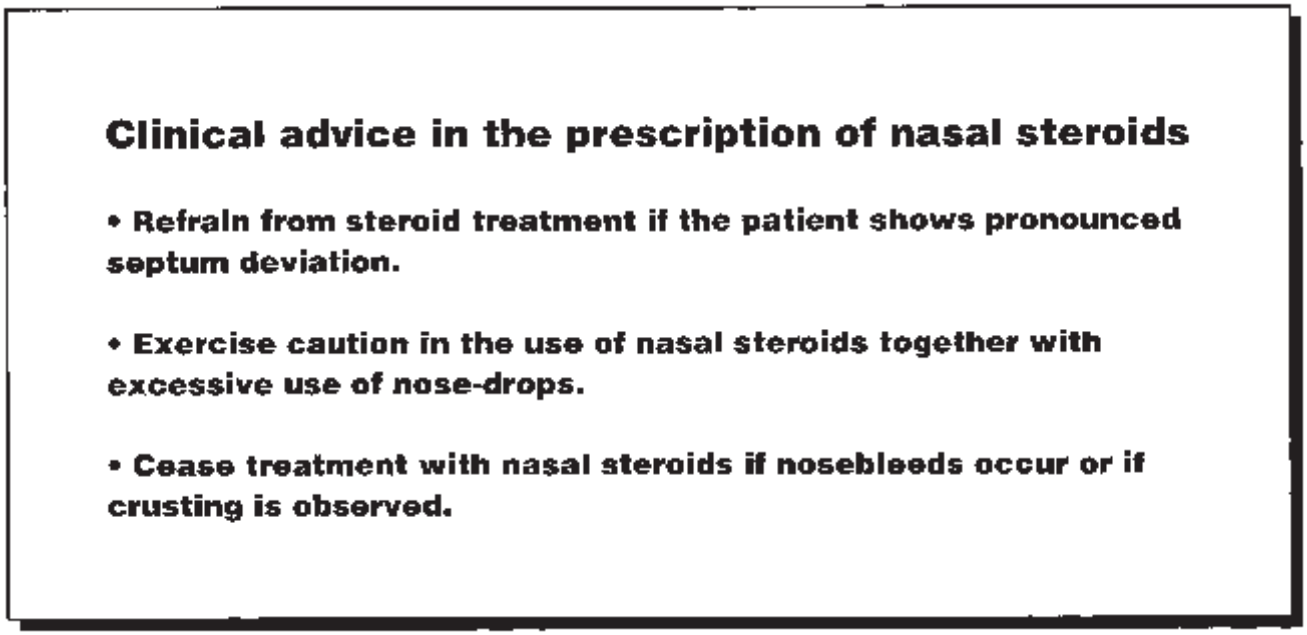

Figure 2. Clinical advice in the prescription of nasal steroids.

bleeding are the typical symptoms. Case 1 demonstrates exposure to the drug with side-effects and withdrawal of the drug with healing of the mucosa, followed by re-exposure with a return of the same side-effects. It appears that the mechanichal trauma of the nasal spray has little to do with the side-effects as the patient has now tolerated a levocabastine spray for several years. Three years before the described episode case 1 had used beclomethasone nasal spray without side-effects. She has also continued to use budesonide for the lower airways without experiencing side-effects. The latter suggests that contact allergy to the steroids used are not the cause. Taken together, the facts suggest that the possible vasoconstricitve effect of steroids is the most plausible explanation. Case report 2 illustrates that a large perforation may develop in a relatively short period of

time. The patient was tested (skin prick test) for contact allergy to budesonide but the result was negative.

DISCUSSION

Are nose-drops a risk factor?

Of the 11 patients who regularly used nasal steroids prior to the diagnosis of septum perforation, 5 reported long-term excessive use of nose-drops. These patients felt that the effect of their steroid spray was insufficient and thus also used vasoconstrictive nose-drops, especially at night. Various brands of nose-drops were involved. Whether it is the nasal steroids, the vasoconstrictive nose-drops, or a combination of both, which caused the septum perforation is impossible to say.

Three of the 11 patients have an obvious septum deviation, and this may possibly be regarded as a risk factor in the long-term use of steroid sprays.

Five of the patients, who had not used nose-drops, and who had no signs of septum deviation, developed moderate to large septum perforations relatively quickly (3, 3, 9, 12 and 20 months) after commencing treatment with nasal steroids. The cause here seems to be clear, although the mechanism is not. Already after a few weeks or months of use, some patients experienced bleeding and crusting in the nose. Despite this, they continued to use their steroid sprays, and after several weeks further use, the mid part of the septum cartilage had been destroyed. The nasal mucosa was extremely irritated with severe crusting.

Vasculitis tests (pANCA, cANCA, Goodpasture's antibodies) proved negative and biopsies from the edges of the septum showed chronic inflammation. In these patients, treatment with steroids was stopped and they were treated with saline solution rinsing of the nose and fusidic acid cream (Fucidin™ Lövens Pharmaceuticals, Malmö, Sweden). If allergic nose-blocking persisted, treatment with peroral antihistamines was initially introduced. The mucosa healed after 4 to 6 weeks, and the remaining perforation was free from irritation.

Septum perforation following treatment with steroids is a well-known complication. In FASS (The Swedish Drug Compendium) septum perforation is described as an uncommon side-effect <1/1000. According to the Swedish Medical Products Agency's statistics, approximately one septum perforation is reported per 4 million DDD. Based on the results of our investigation, there is reason to believe that septum perforation is under-reported. Perhaps a newly reported perforation is not always connected with steroid use, or physicians may not regularly examine the nasal passages of patients undergoing continuous intranasal steroid treatment. Another explanation may be that physicians do not report the perforation as it is a known side-effect. We believe that it is important that all cases of pharmaceutical-induced septum perforation be reported to the relevant pharmaceutical regulation authority in order to give a correct picture of the extent of the problem.

Unknown aetiology

The cause of septum perforation is unknown. However, the mechanism may well be that the intra-nasal steroid spray or powder leads to crusting of the nose, which in turn leads to nosepicking and a mechanical trauma to the mucosa and cartilage. Nosepicking was one of the questions in the questionnaire and was denied by all except one. However nosepicking may not be a habit one admits to easily. The question is nevertheless, why some patients react with crusting of the nasal mucosa upon steroid challenge.

Several explanations are possible. It may be speculated that the contraction of blood vessels due to the action of steroids as has been described in the skin by Thune, (1972) may have an effect on the supply of blood and nutrition to the mucous membrane and cartilage of the septum. Concurrent treatment with vasoconstrictive nose-drops may increase the risk of mucous membrane damage. Four of the 5 patients with septum perforation who reported excessive use of nose-drops in our study were women. This may account for the over-representation of women in the material, as there is no difference between the sexes regarding the prescription of nasal steroids (Fig. 1). On the other hand, no study has demonstrated a vasoconstrictive effect of steroids in the nasal mucosa, using either the 133Xenon washout technique or nasal peak flow measurements (Bende et al., 1983, Lindqvist et al., 1989). However a more sensitive method of measuring mucosal blood flow such as the Laser Doppler flowmetry may be necessary to investigate the possible vasoconstrictive effect of nasal steroids.

Another possibility may be a contact allergic reaction to the steroid component. It is well-known that budesonide, and even other steroids, can cause contact allergies on the skin and mucous membranes, and several cases have been reported (Gamboa et al., 1991, Iglesias-Cadarso et al., 1994, Jerez et al., 1990, Peris-Tortajada et al., 1991, Sastre and Ibanez, 1992). Neither can it be ruled out that some other component of the spray may act as a contact allergen. However, steroid nasal spray in powder form not containing additives or preservatives also seems to cause perforation, which indicates that preservatives or other additives are not the most important factor.

Another possible explanation may be the atrophic effect of steroids on skin and mucous membranes. Reports on the possible atrophic effect are lacking. The authors have only found one Norwegian multicentre study from 1986, in which 50 patients were studied by biopsy one year after commencing treatment with nasal budesonide. The study did not find any signs of mucous membrane atrophy (Lindqvist et al., 1986).

Mechanical damage caused by the act of spraying may explain the cases of perforation in patients with siginificant septal deviation, but does not explain the other cases or the cases using powder.

A more speculative hypothesis is that the steroids facilitate subclinical infection in the nasal mucosa, which leads to the destruction of the mucous membrane and cartilage.

Inform the patient

The risk of perforation appears to be greatest during the first 12 months of treatment. This has a bearing on the way in which

the physician should monitor his patients. A repeat visit, 4 to 6 weeks after the commencement of treatment, is recommended. If there are signs of bleeding or especially crusting, medication must be stopped.

Septum perforation may be free of symptoms, but many patients suffer from crusting, recurrent nosebleeds, and sometimes a whistling noise which can be extremely irritating. Surgical treatment of septum perforations is often needed to relieve the symptoms. With the right surgical technique the results are usually favorable although reperforations occur. (Schultz-Coulon, 1997).

In order to reduce the risk of steroid-induced septum perforation, the inside of the nose should always be examined before treatment is initiated. A pronounced septum deviation may be a contraindication for treatment. Septoplasty should be considered for these patients. Other structural causes for impaired nasal breathing, not susceptible for steroid treatment should be considered, such as unilateral choanal atresia, concha bullosa and hyperplastic inferior concha. Concurrent, long-term use of nose-drops should be noted. Patients being treated with nasal steroids should be examined regularly during the first year of treatment, and both the patient and the doctor should be observant regarding symptoms which may indicate ulceration of the septum and septum mucous membrane. Patients should be informed that upon suffering nosebleeds or crusting they should cease using nasal steroids and consult their doctor. If these safety measures are taken, intranasal steroids may be used as a very reliable and effective method of treating allergic and vasomotor rhinitis.

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