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Influence of topical steroid treatment on maxillary sinusitis

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SUMMARY

The clinical efficacy and adverse effects of budesonide administered as a nasal aerosol in addition to sinus washings and erythromycin therapy was assessed by comparison with placebo in a randomized, double-blind study of 40 patients with chronic or recurrent maxilla,y sinusitis. Most of the patients had been referred for operative treatment. Corticosteroid therapy, 400 µg daily, or placebo was continued for 3 months. Budesonide and antral irrigations reduced nasal symptoms more effectively than placebo, and there was a significantly greater reduction in facial pain and sensitivity in the budesonide group than in the placebo group. During the treatment period, mucosa! thickening as evaluated by radiology decreased more clearly in the budesonide group than in the placebo group, but the difference did not reach statistical significance. The most frequently isolated bacteria were Staphylococcus aureus, Staphylococcus epidermidis and Haemophilus influenzae. Only 2 of 20 Haemophilus strains were ./3-factamase producers. The cellular picture was dominated by neutrophils in all secretions. There was no significant difference in clinical outcome between the two groups. Topical steroid therapy did not cause any adverse effects.

INTRODUCTION

Allergic reaction of the respiratory mucosa is, besides a viral attack, one of the most common causes of disturbed mlicociliary function in the upper respiratory tract. A provoked hypersensitive mucosa responds with hypersecretion and oedema; mucus accumulates and a favourable environment for viral and bacterial infections such as rhinitis and sinusitis is created.

As a rule, therapy for these conditions is primarily focussed on bacterial control by antibiotics and on active removal of bacteria and pus by antral lavage. On the other hand, it is important that the mucous membranes and ciliary function are to

be restored to normal as soon as possible, to avoid recurrence or development of chronic sinusitis. In this study, an attempt was made to enhance the normalization process by topical steroid treatment in addition to ordinary therapy.
The aim of the study was to assess the clinical efficacy and possible side effects of budesonide by comparison with placebo in patients with recurrent or chronic maxillary sinusitis. The active drug or placebo was administered as a nasal aerosol in addition to erythromycin treatment and antral lavages.

PATIENTS AND METHODS

The trial was carried out as a randomized, double-blind, parallel-group study in 40 patients with recurrent or chronic maxillary sinusitis, referred for possible operative treatment to the Department of **O.R.L.** of the Central Hospital at Jyvaskyla (Finland). For adults suffering from chronic or recurrent maxillary sinusitis the Caldwell-Luc procedure was used only as surgical procedure. A diagnosis of recurrent or chronic sinusitis was accepted, if the patient had had at least two verified sinusitis episodes per year during the last two years, and/or ongoing sinusitis for one month with mucous or: ucopurulent secretion in the sinus. Patients under 16 years of age were not accepted. The other exclusion criteria were: (1) antimicrobial therapy within the preceding 10 days; (2) topical and/or systemic steroid therapy within the preceding 30 days; (3) nasal polyps; (4) history of dental sinusitis or diagnosis of dentogenic sinusitis; and (5) hepatic dysfunction. An ethmoiditis, viz. ethmoiditis polyposa, without clearly visible polyps, was not considered as an exclusion criteria and this kind of disease was not registered differently.

First visit

The diagnosis was based on presenting symptoms and signs, careful history taking, and results of antral lavage at the first visit. Samples of sinus secretion were collected from the lavage content for bacteriological analysis and cytological examination. On the same occasion, the severity of symptoms was evaluated and recorded on a scale from 0-3. Radiological examination of the sinuses was performed by standard occipitomental, occipitofrontal and lateral projections and the findings, expressed as opacification percentage, were calculated according to the degree of mucosa! thickening in relation to the total width of the sinus (Revonta et al., 1982). A blood sample was taken for determination of total IgE by means of **RIST.**

Treatment regimen

In addition to regular (7-day) treatment with erythromycin, the patient was given either budesonide aerosol or placebo for three months. The dosage of budesonide (Rhinocort®) was 2 actuations in each nostril b.i.d., that is 400 μg daily.

Placebo aerosol was identical with the active aerosol without budesonide. Erythromycin (Ery-Max®; 250 mg/capsule) was given for 7 days, either 250 mg thrice daily (body weight< 50 kg) or 500 mg twice daily (body weight> 50 kg). Medication taken by patients for other chronic illness was continued. Nasal decongestant or disodium cromoglycolate were not allowed.

Subsequent visits and evaluation of therapy

The efficacy of the treatment was evaluated at three subsequent visits on days 7, 14 and 90 after the start of medication. Symptoms were evaluated and scored, and antral lavage was performed. Samples for bacteriological analysis were again taken on the third visit (day 14) and on the final visit at day 90. Radiological and cytological examinations were repeated on the final, 3-month visit.

Results were analyzed using the two-sample Wilcoxon test for comparison between treatment periods, and signed rank tests for changes within the groups.

RESULTS

Patients' data are given in Table 1. The two groups were well-matched with regard to age, sex, height and weight. Episodes of sinusitis had been more frequent in the placebo than in the budesonide group during the last two years, but the difference was not statistically significant ($p = 0.13$). Thirty-eight of the 40 patients completed the trial. Two patients, one in each group, had to be withdrawn as a Caldwell-Luc operation was performed before the completion of the 3-month treatment period. Eleven of the patients had 22 other diseases, mostly cardiac diseases (17 of 22). Medication mainly consisted of nitroglycerin or its derivatives, digoxin, diuretics, and anti-hypertensive medicines.

Table 1. Patients' characteristics.

		budesonide	placebo
total enrolled (no.)		20	20
sex (male/female)		9/11	10/10
age (years)	mean	45.6	45.2
	range	19-79	24-76
no. of sinusitis episodes within the last 2 years	mean	2.5	3.9
	range	1-12	1-10
no. of antral lavages within the last 2 years	mean	9.6	10.0
	range	1-30	2-30
no. of treatments with antibiotics within the last 2 years	mean	4.1	5.2
	range	0-15	1-20

Symptom scores

There was a greater and more rapid reduction in nasal symptoms in the budesonide than in the placebo group. No significant differences were found in the scores for nasal blockage, nasal discharge and postnasal drip between the two

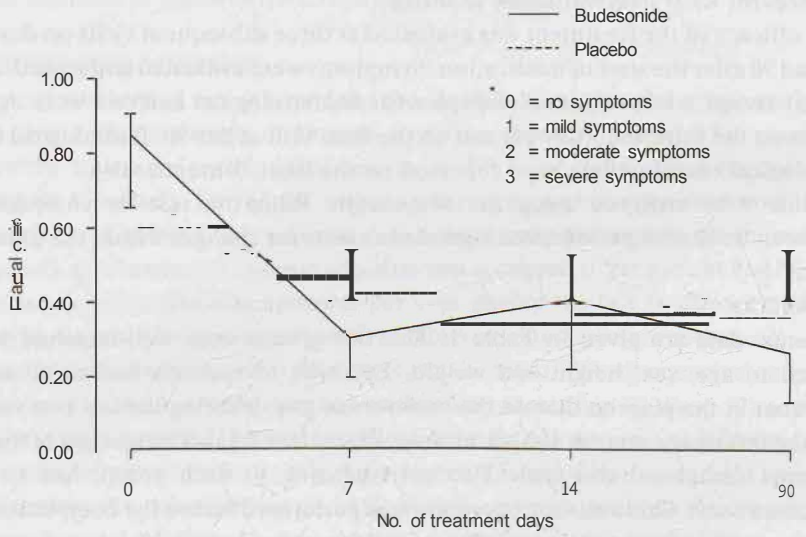

Figure 1. Mean scores(± SEM) for facial pain in 40 patients with chronic sinusitis during 3-month treatment with budesonide/placebo.

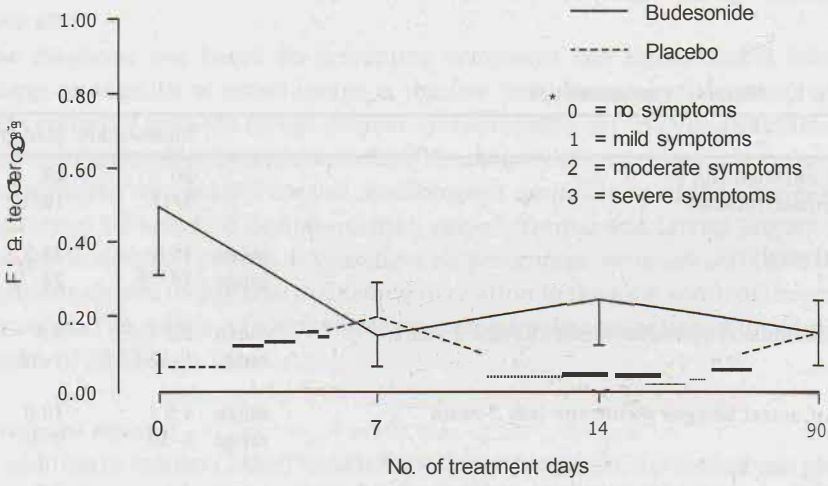

Figure 2. Mean score (± SEM) for facial sensitivity during 3-month treatment with budesonide/placebo in 40 patients with chronic or recurrent maxillary sinusitis.

treatment groups. Compared with pretreatment scores, there was a significantly greater reduction in facial pain and sensitivity in the budesonide group than in the placebo group during the treatment period. In the budesonide group, the mean facial pain decreased from 0.85 to 0.26 (p=0.001), and the mean facial sensitivity score from 0.50 to 0.16, at p = 0.054 (Figures 1 and 2). Budesonide was significantly more effective than placebo in reducing facial pain (p = 0.38) and facial sensitivity (p =0.01). The score for coughing was reduced from the pretreatment mean of 0.65 to 0.21 in the budesonide group (p=0.018).

Radiological findings

Pretreatment antral lavage was positive for sinus secretion in 58 sinuses, viz. in 31 for the budesonide group and in 27 for the placebo group. Radiological findings in these sinuses before and at the end of the 3-month treatment period are presented in Tables 2 and 3. Mucosal thickening decreased more clearly in the budesonide group; the proportion of sinuses with 50% mucosal thickening was

Table 2. Radiological findings in 40 patients with chronic or recurrent maxillary sinusitis. Degree of mucosal thickening at the start of topical steroid/placebo treatment for 3 months.

degree of mucosal thickening	budesonide*		placebo*		total*	
	n	%	n	%	n	%
0- 25%	1	3	3	11	4	7
26- 50%	10	32	8	30	18	31
51- 75%	7	23	6	22	13	22
76-100%	13	42	10	37	23	40
total	31	100	27	100	58	100

* n = number of sinuses;
%= percentage of all sinuses in the respective treatment group and of the sums of the sinuses in the two groups.

Table 3. Degree of mucosal thickening at the 3-month check-up.

degree of mucosal thickening	budesonide*		placebo*		total*	
	n	%	n	%	n	%
0- 25%	14	45	9	33	23	40
26- 50%	6	19	5	19	11	19
51- 75%	3	10	6	22	9	16
76-100%	8	26	7	26	15	25
total	31	100	27	100	58	100

* n = number of sinuses;
%= percentage of all sinuses in the respective treatment group and of the sums of the sinuses in the two groups.

reduced from 65% to 36%. In the placebo group, the corresponding figure at the end of the trial was 48%. The difference in favour of budesonide did not reach statistical significance.

Clinical outcome

The outcome as judged clinically at the end of the trial did not differ significantly petween the tw<? treated roups (Table 4). Antral lavage was positive in 12 patients arid there were altogether 17 unhealed sinuses in the budesonide group, including the patient who had a Caldwell-Luc operation before the end of the trial. During follow-up for one year after the end of the trial, Caldwell-Luc operations were performed on another 7 patients in the budesonide group and altogether 40% (8 of 20) were operated on. The corresponding figures in the placebo group were 50% (10 of 20 patients) and for the whole group 45% (18 of 40 patients).

Table 4. Clinical outcome after 3 months of therapy with budesonide or placebo in addition to sinus washings in 40 patients with chronic or recurrent maxillary sinusitis.

	budesonide				placebo				all			
	sinuses		patients		sinuses		patients		sinuses		patients	
	n	%	n	%	n	%	n	%	n	%	n	%
healed	14	45	8	40	12	44	8	40	26	40	16	40
unhealed	17	55	12	60	15	56	12	60	32	60	24	60
total	31	100	20	100	27	100	20	100	58	100	40	100

Sinus bacteriology

Bacteria were cultured from 44 (76%) of 58 pretreatment specimens, 36 of them showing one single isolate. The most common pathogenic bacteria were *Haemophilus influenzae* (9 isolates) and *Staphylococcus aureus* (9 isolates). None of the *Haemophilus* strains produced /J-lactamase.

Of all 51 specimens taken two weeks after the start of treatment, 37 were positive for bacteria, 28 (55%) of them for one single species. The most common microorganism, *Haemophilus influenzae,* accounted for 11 isolates, of which two were /J-lactamase producing. The most common bacteria cultured at the end of the treatment period were *Staphylococcus epidermidis, Staphylococcus aureus* and *Haemophilus influenzae.* /J-Lactamase-producing strains were not observed.

Sinus cytology

The cellular pattern was studied at different stages (i.e. pretreatment, at 14 days and at 3 months after the start of treatment) to establish possible correlations with allergy, duration of symptoms, bacteriological findings, clinical course and outcome of maxillary sinusitis (Palva et al., 1976). Cellular findings in 58 speci-

mens taken at the pretreatment lavage are grouped according to clinical outcome at the end of the treatment period in Table 5. Neutrophils were the most predominant cells in all secretions. They were seen in moderate or abundant numbers in 67% of the samples. Lymphocytes and monocytes were found in a few secretions, eosinophils and phagocytes were rare, and giant phagocytes did not occur. There were no significant differences in pretreatment cellular patterns between healed and unhealed sinuses.

Table 5. Inflammatory cell pattern in 58 sinus samples taken during pretreatment antral lavage in relation to healing at 3-month check-up.

	healed sinuses at 3-month check-up		unhealed sinuses at 3-month check-up		all sinuses at 3-month check-up	
cell type	n	%	n	%	n	%
neutrophils:						
none	3	12	0	0	3	5
few	6	23	10	32	16	28
moderate	11	42	11	34	22	38
abundant	6	23	11	34	17	29
lymphocytes:						
none	14	54	7	22	22	36
few	12	46	25	78	37	64
moderate	0	0	0	0	0	0
abundant	0	0	0	0	0	0
eosinophils:						
none	25	96	31	97	56	97
few	1	4	1	3	2	3
monocytes:						
none	5	19	9	28	14	24
few	21	81	22	69	43	74
moderate	0	0	1	3	1	2
phagocytes:						
none	25	96	31	97	56	97
few	1	4	1	3	2	3
sinuses	26		32		58	
patients	16		24		40	

Total IgE and eosinophils in nasal smears

Total IgE was elevated in 4 patients in the budesonide group and in 2 patients in the placebo group at the start of treatment. None of these had eosinophils in their nasal smear. Moderate numbers of eosinophils were observed in one budesonide patient, while a few eosinophils occurred in one budesonide and in two placebo group smears.

DISCUSSION

Inflammation of the nose and paranasal sinuses, which causes swelling of the ciliated respiratory mucosa as well as blocking of the natural ostia, is often followed by secondary infection which again causes further inflammation and stasis. Unless this vicious circle is interrupted, progressive tissue damage will occur. Therefore, treatment should be aimed at controlling the microbial flora by antimicrobial agents, stopping the tissue-damaging inflammatory process by topical anti-inflammatory agents, and improving clearance with topical washings and, possibly, surgery to improve drainage and ventilation (Mackay, 1988).

Chronic maxillary sinusitis is a complex condition, in which allergic reactions in the respiratory mucosa have been implicated as a contributory factor. Topical steroids have been found to be particularly effective in the treatment of nasal polyps, but can be useful also in controlling mucopurulent rhinorrhoea in patients with chronic infective symptoms (Mackay, 1989). An open, multicentre investigation of 163 patients with rhinitis, pharyngitis, sinusitis and bronchial syndrome showed that flunisolide reduced inflammatory and obstructive pathological changes in both upper- and lower airways (Marchiori, 1989).

The patients of the present study had long-standing chronic or recurrent maxillary sinusitis and most of them had been referred for surgery because of intractable symptoms. The severity of their disease is apparent in the radiological findings; only 4 sinuses (7%) showed less than 25% opacification, and the degree of opacification was over 50% in 36 sinuses (62%). One-fourth of the patients had concomitant, mainly cardiovascular, diseases.

Radiological measurement of changes in mucosal thickening was used as one objective parameter of the effect of treatment. Mucosa! thickening diminished more clearly in the budesonide group than in the placebo group (Tables 2 and 3), but the difference between the two groups was not statistically significant. One reason for this is probably the chronic nature of the disease; antral washings and budesonide were no longer sufficient to reverse the changes.

The most frequently isolated bacteria were *Staphylococcus aureus, Staphylococcus epidermidis,* and *Haemophilus influenzae.* The findings are similar to those in earlier reports except that no anaerobic bacteria were recovered in the present series. The recovery rate of anaerobic bacteria varies from 25 to 56% (Brook, 1989). That no anaerobic bacteria were found in the present cultures may simply be due to faulty specimen transportation, techniques or methods of culture. Compared with figures reported in the United States (Syndor et al., 1989), the proportion of p'-lactamase-producing *Haemophilus* strains was very low.

The cytological pattern of sinus secretion at different stages of the disease did not point to any correlations with allergy, duration of symptoms, bacteriological findings, or course and outcome of the sinusitis. As is the case in nasal smears, the infection itself may mask a possible eosinophilia. The cellular picture of the sinus

secretion was predominantly infective. At the end of the 3-month treatment period, neutrophils were seen in moderate or abundant numbers in 72% of the unhealed sinuses. It is possible that a persistent infection, maintaining the inflammatory response, is the most important reason for chronic sinusitis in these cases.

Long-term treatment with oral steroids can slow down or disturb the healing of chronic infections, and may even provoke pulmonary tuberculosis. In fact, infection was earlier considered a contra-indication to topical steroid therapy. In this study budesonide treatment for three months did not cause any adverse effects in patients with chronic or recurrent maxillary sinusitis. The beneficial effects of drainage in cases ofpurulent maxillary sinusitis are well documented (Berg et al., 1990), and it has been convincingly demonstrated that restoration of ventilation is a major factor in the healing process. Although budesonide was combined with antral irrigations, the infection did not resolve. With recent rapid advances in nasal endoscopy, endoscopic surgery on the ostiomeatal unit offers new possibilities for sufficient drainage and ventilation (Stammberger, 1986).

Patients with obstructive nasal polyps were not included in this trial, although topical budesonide treatment along with antral washings might have been of particular benefit in such sinusitis patients. Topical steroid therapy has been shown to reduce the size of obstructive nasal polyps and thus enhance drainage of the sinuses via the ostia.

After the end of the trial, the patients were followed for one year and during this time Caldwell-Luc operations were performed on 8 patients in the budesonide group (40%) and on 9 patients in the placebo group (50%). Thus, final evaluation of the outcome was really possible only after a suffciently long follow-up. Melen et al. (1986) found that the outcome was satisfactory in only 34% of conservatively-treated sinusitis patients, but in as many as 80% of surgically treated patients when results were evaluated 3.5 years later.

In conclusion, in this study the effect of the topical steroid treatment appeared to be very modest, but if one has to offer to patients suffering from recurrent or chronic maxillary sinusitis only a radical Caldwell-Luc procedure, topical steroids can be safely instituted in combination with antral irrigations in sinusitis patients, especially if the patient has a history of allergy, before the decision of radical Caldwell-Luc procedure. Treatment may reduce nasal symptoms, fadal pain and sensitivity more quickly. If symptoms and fluid retention continue, surgery to help drainage and ventilation should be considered.

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