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Clinical and histological study to assess changes in the nasal mucosa in patients with chronic perennial rhinitis comparing sodium cromoglycate and placebo

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SUMMARY

A controlled trial comparing sodium cromoglycate 2% nasal solution against placebo has demonstrated that in patients with severe perennial rhinitis sodium cromoglycate is clinically effective and also that gross histological changes in the nasal mucosa are reversed following treatment for eight weeks with this therapy.

INTRODUCTION

A large number of patients are referred to ENT-clinics with a non-seasonal form of chronic rhinitis in which nasal obstruction is a constant feature. The appearance of the nasal mucosa is variable; in some patients it has the normal pink appearance, in others it is pale almost white and in others red, the latter constricts following the application of adrenaline. Such patients are usually diagnosed as perennial rhinitis on the basis of the history and a triad of symptoms; rhinorrhoea, bouts of sneezing and an almost constant nasal obstruction. The disease has usually been present for a number of years and many patients develop a nasal neurosis which adds to the difficulties in treatment. Yet another problem in the management of these cases is the fact that there has often long term abuse of vaso constricting agents and topical antihistamines which in time produce rhinitis medicamentosa.

The aetiology of perennial rhinitis is variable. In many cases it is undoubtedly due to an allergic reaction, however, other factors are important. Oestrogens are known to affect the nasal mucosa, both physical and chemical agents particularly atmospheric pollution cause inflammatory changes, cystic fibrosis of the pancreas (mucoviscidosis) often involves the nose and paranasal sinuses with formation of polyps, finally there is a group labelled vasomotor in whom there is an inbalance of the antomic nervous system.

A number of reports have appeared concerning the use of sodium cromoglycate (SCG) in the treatment of perennial rhinitis, it has been used as a powder (Rynacrom) (Hopper and Dawson, 1972; Thorne and Bradbeer, 1972) and a solution (Lomusol) (Holopainen et al., 1975; Lobaton et al., 1975). The trials have been of short duration and the effect of treatment based primarily on patient response. There are no specific reports on changes in the nasal histology after medium term treatment. The object of this study was to assess the histological and clinical changes which occurred after four weeks and eight weeks treatment with SCG in a group of patients diagnosed as severe intractable perennial rhinitis.

METHODS AND MATERIALS

The trial was designed as a double blind group comparative study of eight weeks duration. Each patient was randomly allocated to one of two treatments; the active solution was 2% aqueous solution of SCG with BKC and EDTA as preservatives, the placebo contained only the preservatives. All patients were instructed to apply the solution by means of a special metered device four times daily thus the active group received a total daily dosage of approximately 21 mg of SCG.

The randomisation was such that $\frac{2}{3}$ of the subjects received active and $\frac{1}{3}$ placebo. Initially 30 patients were selected the diagnosis being Perennial Rhinitis. Patients were rejected if they had a seasonal allergic rhinitis, nasal polyps, infection particularly of the sinuses and those who had within one month of entry into the trial been treated with corticosteroids.

During the trial patients were forbidden to use vasoconstrictors, any type of antihistamine or anti-inflammatory drugs any of which could disguise the results.

Assessment of response was based on two parameters. Firstly, clinical symptoms as recorded by the patient on a daily card; each patient recorded the symptoms of nasal obstruction, rhinorrhoea and sneezing on a scale 0 = no symptom, 1 = mild, 2 = moderate, and 3 = severe. Secondly, histological data was obtained by comparing a pre-trial biopsy with a biopsy taken at four weeks and at eight weeks. The biopsy specimens were obtained from the inferior turbinate fixed in 10% formalin for 8–12 hours then passed through alcohol and toluene and embedded in paraffin. The paraffin blocks were cut in a sliding microtome to a thickness of 5–6 microns and stained with Haematoxylin and Eosin.

Microscopically we studied the following, the condition of the epithelium and mucus glands, the size of the blood vessels, the degree of chronic inflammatory cellular infiltration, the number of goblet cells and eosinophils. Each histological parameter was graded according to the following classification.

Epithelium		*Vessels*	
Normal	– 0	Normal size	– 0
Slight loss in continuity	– 1	Dilated	– 1
Much loss in continuity	– 2	Sinusoidal	– 2
Complete atrophy with erosions	– 3	Haemorrhages present	– 3
Cellular infiltration		*Eosinophils phf*	
Nil	– 0	0	=0
Slight with few cells	– 1	1– 5	=1
Moderate number of cells	– 2	6–10	=2
Marked	– 3	10+	=3
Glands		*Goblet cells phf*	
Normal and abundant	– 0	0	=0
Abnormal and scarce	– 1	1–4	=1
Grossly abnormal	– 2	5–8	=2
		8+	=3

Finally, the general condition of the nasal mucosa was assessed by anterior rhinoscopy at each visit, particular attention was paid to colour, oedema and mucus present.

RESULTS

Of the original 30 patients selected for the trial half had to be excluded, there were ten in the active group and five in the placebo. Seven patients did not return for review at four weeks and a further four dit not return at eight weeks; in the other four the trial was completed but it was not possible to assess the biopsy specimen due to the small size of tissue. Thus the final assessment is based on ten patients receiving SCG and five placebo.

From the initial rhinoscopy it was noted that the patients could be classified into two groups based on the appearance of the mucosa. The majority (Group A) had a pale pink mucosa with varying degrees of oedema with areas of atrophic mucosa, these patients were those who had a long history and consequently a multitude of previous therapy; five patients (Group B) presented with a pale almost white mucosa with slight oedema. On breaking the code it was noted that half the patients in Group A received SCG and half placebo, however all patients in Group B were treated with SCG.

The clinical assessment is shown in Table 1. This is based on the colour of the mucosa and degree of oedema at four and eight weeks.

The evaluation of the patient diary scores for symptoms of rhinorrhoea,

sneezing and blocking have been based on the mean weekly score at Week 1, Week 4 and Week 8.

Table 1. Clinical Assessment.

	group A				group B	
	SCG		Placebo		SCG	
	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks
No change	5	1	5	5	0	0
Improved	0	2	0	0	2	0
Normal	0	3	0	0	3	5

Table 2. Mean Weekly Diary Card Scores.

	SCG			placebo		
Week	1	4	8	1	4	8
Blocking	8.2	8.2	4.9	9.3	10.0	6.8
Rhinorrhoea	10.4	6.0	3.7	10.1	9.3	7.1
Sneezing	7.0	3.5	3.6	7.2	5.4	4.0
Total Nose score	25.7	17.8	12.3	26.6	24.6	18.0

There was a reduction in scores in the SCG for rhinorrhoea and sneezing after four weeks but that blocking had not changed, however after eight weeks therapy all symptoms had decreased. There were very small changes at Week 4 in the placebo group and only a slight improvement by Week 8. The total nose score for the SCG showed at Week 4 a 30% improvement and at Week 8 52%; in the placebo group the changes were 7.5% at Week 4 and 32% at Week 8. The histological data is presented in Table 3.

Table 3. Histology Scores.

	epithelium		infiltration		glands		blood vessels	
	SCG	Pl	SCG	Pl	SCG	Pl	SCG	Pl
Biopsy I								
Baseline	2.4	0.8	1.4	1.4	0.9	0.4	1.3	2.0
Biopsy II								
4 weeks	1.4	0.4	1.6	0.6	0.1	0.4	2.0	1.0
Biopsy III								
8 weeks	0.7	1.0	0.5	1.4	0.3	1.2	2.0	3.0

The baseline scores for the condition of the epithelium was very different in the two treatment groups, however, the placebo group did not change whereas the active group showed a gradual improvement. With regard to the cellular infiltration no change was observed in the active group at four weeks but at

eight weeks there was considerably less infiltration, within the eight week period the placebo group dit not change. The mucus glands improved with SCG and in the placebo group there was a deterioration. The blood vessels in both groups became more dilated in the SCG group and reached a maximum score in the placebo group.

We have looked at the histological change in two separate groups of patients on SCG. The first is those who had a marked infiltration of eosinophils in the mucosa and submucosa, or normal epithelium or moderate erosion. In this group there was a total resolution of the inflammatory infiltration with some improvement in the state of the epithelium.

The second histological group consisted of sections which showed erosion atrophy or metaplasia of the epithelium with a non-specific inflammatory infiltration, gross abnormality of the mucus glands and fibrosis in the corium. The results of SCG treatment were that in some patients the epithelium became pseudo stratified with numerous goblet cells and the infiltration resolved, in other cases the state of the epithelium dit not improve but the state of the mucus glands did and the infiltration resolved.

DISCUSSION

As perennial rhinitis is usually a disease state which continues for a number of years it is to be expected that chronic inflammatory changes will occur; in this group of patients cellular infiltration was often present so that a mean score of 1.4 was present pre-trial in both groups; by the eighth week this had reduced considerably in the SCG group but not in those on placebo. SCG is not an anti-inflammatory agent but exerts its action primarily on the mast cell membrane thus inhibiting the release of pharmocologically active substances. One must assume therefore that by its action on the mast cell SCG prevents tissue damage by histamine SRS and other substances and thus allows the normal host defence mechanisms to resolve the chronic inflammatory changes. It is also considered likely that the improvement noted in the state of the epithelium and glands is also not directly due to SCG.

The symptoms of blocking which predominates in many of these patients could be due to two factors; one is the thickening of the submucosa following cellular infiltration, the other is the thick mucus produced by an increase in the number of goblet cells in the mucous membrane. It was noted that this symptom was not noticeably improved until the eighth week on SCG whereas rhinorrhoea and sneezing both showed improvement by Week 4. The clinical symptoms therefore suggest that improvement in the major complaint depends on resolution of the chronic inflammatory changes present.

In those patients in whom eosinophils were present in large numbers and therefore in whom the diagnosis is allergic perennial rhinitis, the histological resolu-

tion was generally complete and this is to be expected with the use of an anti-allergic drug. In those patients without eosinophilia the value of SCG was less conclusive, nevertheless some did show an improvement which may indicate that SCG has a place in the therapy of non-proven perennial rhinitis. Exactly why this should be is not clear unless it implies that SCG has an effect on cells other than mast cells.

The conclusion, therefore, is that SCG is a very useful drug for the treatment of severe perennial rhinitis but particularly so in those who are classified as allergic. Results are not always dramatic, particularly when gross pathological changes have occurred over a period of time and in general we therefore recommend at least eight weeks therapeutic trial.

RESUMÉ

On décrit les resultats cliniques et les donnés histologiques obtenus avec le traitement de patients affectés de rhinitis persistent avec inhalateurs de DSCG et un placebo.
Cet étude a eté fait pendant huit semaines et par le méthode du double-aveugle.
On a contrôlé tous les patients au début, a la 4ème semaine et au final du traitement, avec valoration clinique et mini-biopsie de la muqueuse nasale.

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