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Nasal airflow in growth hormone treatment*

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SUMMARY

Nasal congestion due to hormonal influences has been recognised as a clinical entity, and a "hormonal rhinitis" has been proposed to occur in acromegaly. In this study we investigated the effect of low-dose recombinant human growth hormone over eight weeks on nasal congestion as measured by nasal peak flow in a randomised, placebo-controlled, double-blind cross-over clinical trial in ten patients with short bowel syndrome. The treatment did not induce a significant nasal congestion. Whether higher doses as used in many catabolic conditions do remains to be determined.

Key words: nasal congestion, growth hormone, peak expiratory flow

INTRODUCTION

Nasal congestion due to hormonal influences has been recognised as a clinical entity, briefly mentioned in the International Consensus Report on the Diagnosis and Management of Rhinitis in 1994 (Lund et al.). Hypothyroidism can cause hormonal rhinitis (Gupta et al. 1977).

Pregnancy rhinitis was first described by MacKenzie in 1898. The pathogenesis has been debated since then, as reviewed by Derkay 90 years later (1988). Increased serum levels of estrogen has been the most plausible explanation model, initially fully supported by Mabry (1983), but in a later review attention was directed to the importance of rhinitis medicamentosa (Mabry, 1986). Other theories include long-standing sinusitis, which in pregnancy may give no other symptom than nasal congestion (Sorri et al., 1980), emotional and physical stress (Holmes et al, l950), and elevated circulating blood volume, leading to increased nasal vascular pooling which also could be aggravated by progesterone-induced nasal vascular smooth muscle relaxation (Schatz and Zeiger, 1988).

The early contraceptive pills, containing high levels of estrogen, had nasal congestion as a side effect. However, nasal congestion during menstruation, a phenomenon also first described by MacKenzie (1884) is not caused by increased serum levels of estrogen, as we have shown previously (Ellegård and Karlsson, 1994).

A "hormonal rhinitis" has been proposed to occur in acromegaly (Lund et al., 1994). Growth hormone (GH) is normally secreted in episodic bursts with low or undetectable levels between peaks. Peptide growth factors, especially insulinlike growth factor I (IGF-I) have been linked to regenerative activity in nasal mucosal cells (Hansson et al, 1991). Furthermore IGF-I has been associated with formation of nasal polyps (Petruson et al., 1988). IGF-I and IGF binding protein 3 (IGFBP-3) are associated with the secretion of GH. Recombinant human growth hormone (rhGH) has been used primarily for substitution in GH-deficient children and adults (Salomon et al., 1989), but in later years also in catabolic conditions (Ziegler et al., 1994), and in conjunction with total parenteral nutrition (Ziegler et a1., 1992). Treatment with rhGH in substitution doses has sometimes been associated with side effects such as water retention, edema, and atrial fibrillation (Bengtsson et al., 1993), but to our knowledge, no effects of rhGH on the nasal mucosa or nasal air flow have been reported.

The principal aim of this study was to investigate the effect of low-dose recombinant human growth hormone on nasal congestion as measured by nasal peak flow in a randomised, placebo-controlled, double-blind, cross-over clinical trial. Another aim was to ascertain whether the treatment would induce any change in lung function.

SUBJECTS AND METHODS

The detailed protocol, including treatment effects on body composition, has been reported recently (Ellegård et al., l997). Ten patients, three female and seven male, mean age 49 (range 30-72 years), with short bowel syndrome for more than one year because of Crohn's disease were included in the study. Mean body weight was 56 kg (range 46-69 kg), mean body height 1.74 m (range 1.61-1.89 m) and mean body mass index 18 kg/m^2 (range 16-21 kg/m^2).

The patients had no history of chronic rhinosinusitis or bron-

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chial asthma and they had no nasal complaints upon entry. The duration of the treatment periods with rhGH / placebo was eight weeks with a minimum of twelve weeks washout periods in a randomised, placebo-controlled, double-blind, cross-over protocol. rhGh (Genotropin Kabi Pharmacia, Stockholm, Sweden) was administered subcutaneously at a dosage of 24 μg/kg/day. The placebo vials contained the same vehicle and were visually indistinguishable. Patients were hospitalised for five days at the beginning and at the end of each treatment period. The airflow was measured on four consecutive mornings during each of these periods. Nasal airflow was quantified by nPEF (= nasal Peak Expiratory Flow) with patients in an upright position, after 20 minutes rest, three times on each occasion, using a mini-Wright peak flow meter (Clement Clarke, Harlow, England) connected to an anaesthetic mask covering the nose (MIE, nr 1 or 2, Exeter, England). All registrations were supervised by the same physician (L.E.). After the nPEF, the patients also performed ordinary oral PEF. The nPEF and PEF values were expressed in l/min and were rounded off to the nearest 10 l/min. For every occasion, the maximum value of the three registrations was used in later statistical analysis, as we have discussed earlier (Ellegård and Karlsson, l994). The "Blockage Index" (BI=(PEF-nPEF)/PEF) according to Taylor (Taylor et al., 1973) was used as an objective assessment of nasal obstruction, where rising index indicates increasing obstruction. Patient sera were collected before and after each treatment period, stored at –20°C until analysed in one batch each for IGF-I and IGFBP-3 by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The mean values of each four-day period regarding nPEF, PEF and BI were calculated.

Treatment effects during rhGH and placebo periods were evaluated with Wilcoxon's signed ranks test with $p<0.05$ considered to be statistically significant. Spearman's correlation coefficient was used. Values are presented as mean ± standard error of means unless otherwise stated.

We have previously reported a difference of 50 l/min in nasal PEF to be clinically significant (Ellegård and Karlsson, 1994). The number of patients in this cross-over, placebo controlled study was based on our earlier experiences with nasal PEF measurements, where the intra-individual SD was 22 I/min. With a confidence level of 5% this study should be able to detect a difference of 25 l/min with a power of 0.90.

All participants gave their informed consent. The study was approved by the Ethics Committee of Sahlgrenska University Hospital, Göteborg.

RESULTS

All ten patients completed the study. During placebo treatment there were no significant changes in body weight, IGF-I or IGFBP-3. During active treatment with rhGH, body weight increased by 2.3±0.8 kg (p=0.005). Serum IGF-I increased on average 91% from 207±32 μg/l before treatment to 396±65 after (p=0.005) and IGFBP-3 increased 35% from 2.36±0.3 mg/ml to 3.15±0.3 (p=0.005). Mean PEF values were 80% of predicted (range 36-96%, mean value 448 l/min registered / 562 l/min predicted; SEM 25 l/min) (Gregg and Nunn, 1973).

Table 1. Mean values for peak expiratory flow, nasal peak expiratory flow and blockage index (BI=(PEF-nPEF)/PEF) in ten patients before and after eight week treatment periods with rhGH / placebo. No significant changes attributable to rhGH treatment were found.
(x= mean values, SEM= standard error of means).

		rhGH treatment		placebo treatment	
		before	after	before	after
PEF, l/min	x	451	454	429	458
	SEM	43	40	41	42
nPEF, l/min	x	280	275	249	292
	SEM	22	28	30	36
BI	x	0.36	0.37	0.42	0.36
	SEM	0.04	0.06	0.05	0.06

The values before and after treatment with rhGH and placebo are presented in Table 1. There were no significant changes of either nPEF, PEF or BI during rhGH or placebo treatment periods. The intra-individual variation (SD) of nPEF was 19 l/min during placebo treatment.

There were no significant correlations between changes in body weight or concentrations of IGF-I and IGFBP-3 compared with changes in PEF and BI during rhGH treatment.

DISCUSSION

In this randomised, cross-over, placebo-controlled clinical trial, we found no connection between treatment with recombinant human growth hormone and nasal congestion expressed as change in nasal PEF. Neither was there any change in lung function, as expressed by PEF-values, attributable to GH. Blockage index, which compensates for individual variations in lung function, also failed to show any effect of rhGH treatment upon the degree of nasal congestion. Because of the low intra-individual variation in nasalPEF, it would have been possible to detect differences of 22 l/min, which is half of the difference previously found to be clinically significant (Ellegård and Karlsson, 1994).

PEF values were lower than predicted by sex, age and body height, possibly because of low body weight as part of short bowel syndrome, indicating chronic malnutrition and muscle wasting in several of the patients.

We have shown earlier that raised serum levels of estrogen cannot possibly be a causative factor in nasal congestion of menstruation (Ellegård and Karlsson, 1994). The same holds for pregnancy rhinitis (Ellegård and Karlsson, 1997). We suggest placental growth hormone as the hormone responsible for nasal congestion in pregnancy rhinitis. Weight gain, representing retention of water, does not per se seem to induce nasal congestion but there may still be a local retention, i.e. edema in the mucosa.

The theory that growth hormone may induce changes in the mucosa of the upper airways is supported by Skinner and Richards (l988). They report a significantly increased frequency of mucosal hypertrophy and polyp formation in the sphenoid

and ethmoid sinuses of acromegalic patients compared with patients with prolactinoma. No such pathology was found in the nasal mucosa, which, however, was examined after preoperative cocaine treatment.

The results of the present study show that low-dose rhGH treatment over eight weeks does not induce a significant nasal congestion, as measured by nasal peak expiratory flow and blockage index. Higher doses, as used in many catabolic conditions, might however induce more pronounced effects.

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