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The effect of intranasal fluticasone propionate on the diving reflex in patients with non-eosinophilic non-allergic rhinitis*

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SUMMARY

The usual nasal response to head submersion in aquatic mammals is an increase in resistance to airflow, the so-called "diving reflex". Although less well-developed in humans, it is nevertheless present. It is likely to occur due to a relative increase of parasympathetic over sympathetic control of the nasal vasculature. Non-eosinophilic non-allergic rhinitis is thought to be due to a similar imbalance and we have attempted to establish whether the diving reflex is abnormal in this condition and whether intranasal fluticasone propionate for 6 weeks has any effect in modifying the nasal response.

Key words: rhinitis, cold, diving, non-allergic rhinitis, fluticasone propionate

INTRODUCTION

The usual nasal response to head submersion in aquatic mammals is a marked increase in nasal airway resistance (Sherman et al., 1992). This is an adaptive reflex which protects the lower airways. Whilst this reflex is less well-developed in humans, it is nevertheless still present (Sherman et al., 1992). The control of nasal airway resistance depends upon a balance between the parasympathetic and sympathetic control of the nasal vasculature. An increase in parasympathetic tone results in an increase in nasal airway resistance (Jones and Lancer, 1987) and a reduction of parasympathetic tone (e.g., by vidian neurectomy) in a decrease (Golding Wood, 1961). Similarly, increased sympathetic tone leads to a decrease in nasal airway resistance (Malm, 1977), and cervical sympathectomy to an increase (Fowler, 1943). It has been suggested that the primary pathogenesis of non-eosinophilic non-allergic rhinitis (NENAR) is due to an imbalance between the parasympathetic and sympathetic influxes on nasal vasculature (Borum et al., 1979; Mullarkey et al., 1980; Jones and Lancer, 1987). This is in contrast to the non-allergic rhinitis with eosinophilia syndrome (NARES) and allergic rhinitis, in which abnormalities of prostaglandin metabolism are postulated. It would, therefore, seem reasonable to suppose that whilst pharmacological agents which modify prostaglandin metabolism may have an effect in altering reflex control of nasal vasculature in allergic rhinitis and NARES, they would have less of an effect in NENAR.

Diving may be simulated under laboratory conditions by the "cold face test" (Khurana et al., 1980; Heath and Downey, 1990). We have applied this test to study the diving reflex in NENAR before and after treatment with intranasal fluticasone propionate and also in a group of controls.

MATERIAL AND METHODS

The nasal airway response to simulated diving was studied in normal subjects and in patients suffering from NENAR. Normal subjects were recruited from the staff of The Royal Liverpool University Hospital, Liverpool. Inclusion criteria were an absence of symptomatic nasal obstruction, rhinorrhoea, sneezing, allergy, aspirin sensitivity, no previous nasal surgery and normal findings on anterior rhinoscopy. Additional criteria included a non-specific IgE level (RAST) of less than 40 IU/ml and a nasal differential eosinophil count expressed as a proportion of total inflammatory cells present in a well-populated microscopic field of less than 20% (Romero and Scadding, 1992). Those in the NENAR group suffered from two or more of the symptoms of nasal obstruction, rhinorrhoea, sneezing perennially for at least two years, and also had a RAST of less than 40 IU/ml and a nasal eosinophilia count of less than 20%. There were 16 subjects in the normal group, and 18 patients in the NENAR group. There were no significant differences between the groups with respect to age or sex.

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Diving was simulated by means of the "cold face test" (Heath and Downey, 1990). A "gel pack" (Boots Pharmaceutical, UK) cooled to 0°C was applied bilaterally to the forehead for a period of 40 s. Nasal airway resistance was measured by active anterior rhinomanometry both before and after application of the pack. The subject was then given a rest of 3 min before the face mask was adjusted and rhinomanometric assessment of the opposite nostril undertaken. Patients in the NENAR group then received 2 puffs (100 μg) of fluticasone propionate once daily into each nostril for six weeks and were re-assessed.

The results were analysed by non-parametric statistical methods. Approval of The Royal Liverpool University Hospital Ethical Committee was obtained for this study.

RESULTS

Expiratory total nasal airway resistance values in the normal group were compared with those in the NENAR group. The median pre-test expiratory total nasal airway resistance (ETR) in the normal group was 0.357 kPa.s/l (lower 95% confidence interval (CI): 0.320; upper 95% CI: 0.644).

Following application of the cold pack the median value dropped slightly to 0.351 kPa.s/l (lower 95% CI: 0.326; upper 95% CI: 0.590). In the untreated NENAR group, the pre-test median ETR was 0.473 kPa.s/l (lower 95% CI: 0.315; upper 95% CI: 0.591) and the post-test median 0.895 kPa.s/l (lower 95% CI: 0.183; upper 95% CI: 0.568). The median change in the NENAR group was significantly higher than the median change in the normal group (Mann-Whitney two-tailed test; $p<0.05$).

Following treatment with fluticasone propionate the pre-test value in the NENAR group dropped to 0.333 kPa.s/l (lower 95% CI: 0.241; upper 95% CI: 0.657) and the post-test median ETR dropped to 0.379 kPa.s/l (lower 95% CI: 0.312; upper 95% CI: 0.442). These results are illustrated in Figure 1.

The median change in ETR in the pre-treatment NENAR group was significantly higher than the median change in the post-treatment NENAR group (Wilcoxon two-tailed test: $p<0.025$). The median change in ETR in the normal group was not significantly different from the median change in the treated NENAR group.

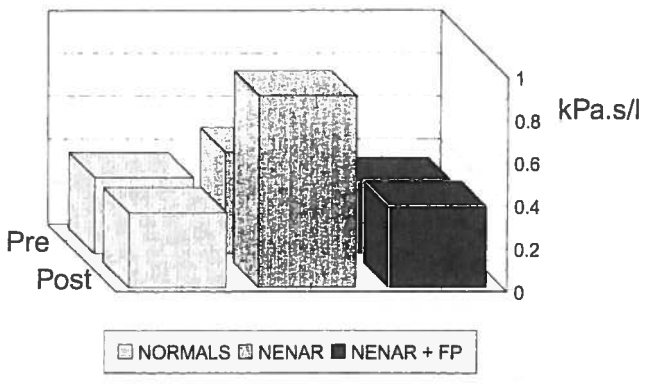

Figure 1. Median change in expiratory total nasal airway resistance (ETR) before and after simulated diving in normal subjects, NENAR and NENAR following treatment with fluticasone propionate.

DISCUSSION

A cold stimulus applied to the face causes bradycardia and peripheral vasoconstriction and may be used to simulate the diving reflex (Khurana et al., 1980). The normal nasal airway response to breathing cold air is known to be an increase in resistance (Drettner 1961; Takagi et al., 1969; Salmon et al., 1971), and the response to simulated diving has more recently been shown to be the same (Sherman et al., 1992). The afferent limb of this reflex is somatic and mediated by the trigeminal nerve. The efferent limb responsible for the nasal airway response and bradycardia is parasympathetic, and that for the peripheral vasoconstriction sympathetic. This reflex, therefore, allows the parasympathetic efferent effects on the nasal vasculature to be studied independently of other afferent or efferent autonomic influences on the nose.

Whilst abnormalities of the autonomic control of nasal vasculature may well be involved in all forms of rhinitis, it would seem likely that such abnormalities are of paramount importance in NENAR (Bodum et al. 1979; Mularkey et al., 1980; Jones and Lancer, 1987). We have previously shown a significantly different nasal airway response to simulated diving in NENAR with respect to a normal control group which would seem to indicate an abnormality of parasympathetic efferent control of the nasal vasculature (Cook et al., in press). We have now further shown that this abnormal response in NENAR may be modified by fluticasone propionate. Whilst it may well be that abnormalities of autonomic control of nasal vasculature may be of paramount importance in NENAR, it would now seem that these effects are mediated by a final biochemical pathway which is shared with allergic rhinitis and NARES.The symptom complex associated with NENAR is probably largely produced by autonomic imbalance (Borum et al., 1979; Jones and Lancer, 1987). Steroids produce most of their pharmacological effect by blocking eicosanoid biosynthesis. It is well known that complex interactions exist between the autonomic nervous system and eicosanoids (Jones and Lancer, 1987), and this could be the explanation for the efficacy of steroids in normalising the nasal hyper-reflexia demonstrated in NENAR.

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