be due to persistence of non-acid-reflux and pepsin causing ongoing laryngeal epithelial inflammation. We investigated: (a) the prevalence of pepsin reflux in respiratory patients requiring nasendoscopy for the investigation of upper airway symptoms; (b) the performance of commonly used clinical LPR-diagnostic tools in predicting the presence of salivary pepsin.

**Methods** Subjects had symptoms and signs of laryngeal inflammation quantified using, the Reflex Symptom Index (RSI) and Reflex Finding Score (RFS). Salivary pepsin was measured with a lateral flow device using monoclonal antibody labelling (Peptest, RDBiomed). Patients with severe signs of laryngeal inflammation were referred for impedance-pH oesophageal studies to assess for objective evidence of reflux.

**Results** Of the 78 subjects recruited, 76% were female, mean age 55 (range 17–82). Ten were undergoing investigation for chronic cough, and 68 for possible vocal cord dysfunction (confirmed in 45). 30 had concomitant asthma, and 42 were prescribed anti-reflux treatment. 87% had a high RSI, and 51% a high RFS. Pepsin was detected in the saliva of 49/78 subjects (63%), and prevalence did not vary significantly between treatment group. There was a weak correlation between the RFS and pepsin concentration (r=0.28, p=0.01) and the positive and negative predictive values for pepsin detection for those with a high RFS were 65% and 69% respectively. To date all 8 patients tested have had significant proximal reflux on impedance study, of which 6 had a positive pepsin assay.

**Conclusion** Salivary pepsin was frequently present in patients with upper airway symptoms, but only weakly related to clinical findings of reflux, suggesting a high prevalence of LPR that is not associated with typical laryngeal findings. The significance of such sub-clinical reflux remains to be seen however the use of pepsin assay in patients with upper airway symptoms may be most valuable in directing diagnosis in milder cases where symptoms and signs lack specificity and the condition may otherwise be missed.

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**P152**

**THE IMPACT OF A SELECTIVE ORAL TRPV1 ANTAGONIST IN PATIENTS WITH CHRONIC COUGH**

doi:10.1136/thoraxjnl-2012-202678.213

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**Background** Increased expression of TRPV1 receptors in the airways of chronic cough patients and heightened cough responses to inhaled capsaicin are suggestive of a role for TRPV1 receptors in chronic cough. We hypothesised that antagonism with a potent, selective, peripherally acting, oral TRPV1 antagonist, such as SB705498, would offer substantial cough symptom control.

**Methods** Subjects had symptoms and signs of laryngeal inflammation quantified using the Reflex Symptom Index (RSI) and Reflex Finding Score (RFS). Salivary pepsin was measured with a lateral flow device using monoclonal antibody labelling (Peptest, RDBiomed). Patients with severe signs of laryngeal inflammation were referred for impedance-pH oesophageal studies to assess for objective evidence of reflux.

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**P153**

**THE IMPACT OF TRPV1 ANTAGONISM ON THE TREATMENT OF SEASONAL ALLERGIC RHINITIS**

doi:10.1136/thoraxjnl-2012-202678.214

1RD Murdoch, 1P Bareille, 1J Bentley, 1K Smart, 1F Horak. ‘GlaxoSmithKline, Stevenage, UK; 2University Clinic, Vienna, Austria

**Background** Topical intranasal steroids are widely considered to be the most efficacious pharmacotherapy for the treatment of allergic rhinitis, and yet, for many, symptoms still remain troublesome. We hypothesise that the residual symptoms are a result of nasal neuronal hyperresponsiveness during the pollen season and should be ameliorated by a topical intranasal TRPV1 antagonist. SB705498 is a selective TRPV1 antagonist shown to produce significant inhibition in animal and human models involving nasal sensory nerves.

**Methods** The study involved 70, male and female, subjects with proven rhinitis in a randomised, double-blind, placebo-controlled, 3-way incomplete block crossover design in a well validated Allergen Challenge Chamber paradigm in Vienna. Subjects received Placebo, FP (200µg), SB705498 (12mg), or FP+498. Subjects were dosed for 8 days, within the pollen season, before being exposed to a chamber challenge on the 8th day. TNSS was the primary endpoint recorded for the 4 hours in the chamber. The comparisons of interest were FP+498 vs. FP, and 498 vs. Placebo. Additional endpoints consisted of symptoms over the 8 days of dosing, Active Anterior Rhinomanometry, Rhinoconjunctivitis QLQ, PK and tolerability. Each period was separated by 14–20 days.

**Results** There was no evidence of a decrease in symptoms with FP+498 compared to FP alone, or for 498 compared to placebo. Statistically significant and clinically relevant reductions in TNSS compared with Placebo were observed at all time points during the challenge for FP and FP+498. The mean (95% CI) reduction in weighted mean TNSS was –2.94 (–3.38, –2.50) for FP alone and –2.28 (–2.79, –1.78) for the combination.
Methods

selective TRPV1 antagonist in animal and human models. It would offer substantial symptom control. SB705498 is a potent topical antagonist with a selective TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Background

TRPV1 is a ligand gated ion channel activated by a range of physiological factors such as temperature, pH, and osmotic stress. In the nose, the TRPV1-expressing sensory c-fibres are thought to play a key role in the development of nasal hyper-responsiveness resulting in symptoms in NAR patients. We hypothesise that topical antagonism with a selective TRPV1 antagonist would offer substantial symptom control. SB705498 is a potent selective TRPV1 antagonist in animal and human models.

Methods

40 M&F NAR patients were enrolled into a randomised, double-blind, placebo controlled, 2 period crossover study of either intranasal SB705498 12mg o.d. for 14 days did not alleviate the symptoms of NAR triggered by the most common provocation agent: Cold Dry Air. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Conclusions

In a robust clinical model of allergic rhinitis, there was no intrinsic activity demonstrated by SB705498 and no additive effect on a background of intranasal steroids. FP was highly effective in this study. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Results

PK analysis supported an o.d. regimen with 2 fold accumulation over the dosing period.

Conclusions

In a robust clinical model of non-allergic rhinitis, intranasal SB705498 12mg o.d. for 14 days did not alleviate the symptoms of NAR. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Abstract P154 Figure 1

P155

VISUALISATION OF AIRWAY NERVES IN CHRONIC COUGH: TOWARDS THE IDENTIFICATION OF THE HUMAN ‘COUGH RECEPTOR’

Introduction

The spinal and vagal innervation of the respiratory tract is well defined, particularly in animals. These discoveries include the identification of pathways involved in provoked cough and descriptions of the guinea pig ‘cough receptor’. However, many of the immunohistochemical features of the airway afferents described in animals have yet to be defined in humans, yet plasticity of these airway afferents may be important in the pathophysiology of chronic cough.

Objectives

To define and characterise the innervation present in bronchoscopic biopsies from patients with chronic cough. We aimed to carry out the first ever whole mount immunohistochemical studies of airway nerves in cough patients, a technique that should improve visualisation of these neuronal structures and their sites of termination.

Methods

Biopsy tissue was gifted from patients undergoing bronchoscopic biopsies from patients with chronic cough. Tissue, sampled from throughout the extrapulmonary airways, was immediately fixed in 4% paraformaldehyde. Non-specific antibody binding was blocked using 10% normal serum and 1% skimmed milk powder, diluted in PBS, before application of primary antibodies. Polyclonal rabbit anti-PGP9.5 (Ultraclone, UK) and monoclonal mouse anti-neurofilament (NF200, Leica Biosystems, UK) were applied at a dilution of 1:1000 and 1:200 respectively. Primary antibody binding was detected using appropriate Alexa-fluor conjugated secondary antibodies and whole mount preparations were visualised using epifluorescence and confocal microscopy. Images of biopsy staining were subject to morphometric analysis.

Results

Many epithelial, subepithelial and intramuscular fibres were detected using both antibodies. Co-staining revealed that only PGP9.5 defined pulmonary neuroendocrine cells and better elucidated varicose epithelial fibres. A proportion of all fibre types were detected using both antibodies. Co-staining revealed that only PGP9.5 defined pulmonary neuroendocrine cells and better elucidated varicose epithelial fibres. A proportion of all fibre types were detected using both antibodies.

Abstract P154 Figure 1

P154

TRPV1 IS NOT A TARGET FOR THE TREATMENT OF NON-ALLERGIC RHINITIS: A CLINICAL STUDY

doi:10.1136/thoraxjnl-2012-202678.215

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Background

TRPV1 is a ligand gated ion channel activated by a range of physiological factors such as Temperature, pH, and osmotic stress. In the nose, the TRPV1-expressing sensory c-fibres are thought to play a key role in the development of nasal hyper-responsiveness resulting in symptoms in NAR patients. We hypothesise that topical antagonism with a selective TRPV1 antagonist would offer substantial symptom control. SB705498 is a potent selective TRPV1 antagonist in animal and human models.

Methods

40 M&F NAR patients were enrolled into a randomised, double-blind, placebo controlled, 2 period crossover study of either intranasal SB705498 12mg o.d. for 14 days did not alleviate the symptoms of NAR triggered by the most common provocation agent: Cold Dry Air. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Conclusions

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PK analysis supported an o.d. regimen with 2 fold accumulation over the dosing period.

Conclusions

In a robust clinical model of non-allergic rhinitis, intranasal SB705498 12mg o.d. for 14 days did not alleviate the symptoms of NAR. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, suggesting redundancy in symptom pathways.

Abstract P154 Figure 1

P155

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P153 The impact of TRPV1 Antagonism on the Treatment of Seasonal Allergic Rhinitis

RD Murdoch, P Bareille, J Bentley, K Smart and F Horak

*Thorax* 2012 67: A128-A129
doi: 10.1136/thoraxjnl-2012-202678.214

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