

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 Reflux Symptom Index (RSI) and Reflux 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 63% 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.

P152 THE IMPACT OF A SELECTIVE ORAL TRPV1 ANTAGONIST IN PATIENTS WITH CHRONIC COUGH

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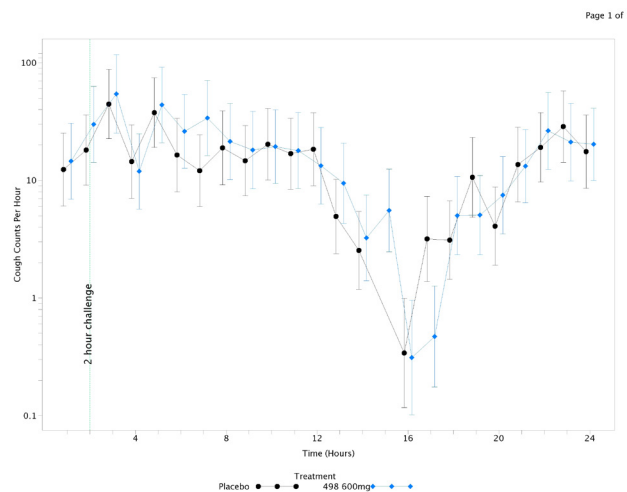
Background Increased expression of TRPV1 receptors in the airways of chronic cough patients and heightened cough responses to inhaled capsaicin are suggestive of a role for TRPV1 receptors in chronic cough. We hypothesised that antagonism with a potent, selective, peripherally acting, oral TRPV1 antagonist,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

Methods 21 patients with unexplained chronic cough (caucasian, 71% female, mean age 53yrs) participated in a double-blind, placebo-controlled, single dose, 2-period, crossover study to investigate the relationship between pharmacokinetic (PK) derived TRPV1 receptor occupancy, change in capsaicin (C5) threshold and 24hr cough count following 600mg SB705498. PK samples were taken over the dosing interval, capsaicin threshold was determined at screening, 2hrs (Cmax) and 24hrs post-dose and 24hr objective ambulatory cough counts were recorded on each dosing day via a cough monitor (vitaloJAK™) with manual counting. In addition, CQLQ and VAS urge to cough was measured. A battery of safety and tolerability measures were also recorded, including core body temperature.

Results TRPV1 receptor occupancy derived from plasma levels and factoring a plasma/lung ratio of 1, was approximately 45% at 2hrs and 25% at 24hrs. This translated to a 4 fold shift in the capsaicin C5 threshold at 2hrs (2uM to 8uM) maintained at 24hrs. However, there was no difference between hourly cough count profiles between placebo and SB705498 (see figure), with hourly counts of

20–30c/h and the characteristic nocturnal reduction. Cough counts were remarkably stable, repeated one month apart and over the 8 months of the study (including winter).

Conclusions We conclude that despite a clear relationship between receptor occupancy and engagement of the TRPV1 receptor as evidenced by the shift in the capsaicin threshold, there was no translation to any clinical efficacy parameter. This suggests peripheral TRPV1 receptor activation is not an important determinant of spontaneous cough frequency in chronic cough and that reductions in capsaicin responses do not necessarily predict anti-tussive effects.



Abstract P152 Figure 1

P153 THE IMPACT OF TRPV1 ANTAGONISM ON THE TREATMENT OF SEASONAL ALLERGIC RHINITIS

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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 (200ug), 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.