Name of Sponsor/Company
University of Dundee

Title of Study
A Placebo Controlled Trial to Evaluate the Effects of Levocetirizine on Nasal Allergen Challenge and Adenosine Monophosphate Challenge In Patients with Intermittent and Persistent Allergic Rhinitis

Study centre(s)
Asthma & Allergy Research Group

Publication (reference)
VAIDYANATHAN S, NAIR A, BARNES ML, MELDRUM K, LIPWORTH BJ. Effect of levocetirizine on nasal provocation testing with adenosine monophosphate compared with allergen challenge in allergic rhinitis. Clin Exp Allergy 2009;39:409-416

Date of first enrolment
November 2005

Date of last completed
December 2006

Objectives
We compared the effect of levocetirizine on nasal adenosine 50-monophosphate (AMP) with specific allergen challenge in patients with intermittent and persistent allergic rhinitis (AR).

Methodology
Patients with AR were randomized in double-blind cross-over fashion to receive single doses of levocetirizine 5mg or identical placebo, with nasal challenge performed 12 h after dosing. Nasal AMP or allergen challenge was conducted on separate days with 1- and 2-week washout periods in between, respectively.
Measurements of peak nasal inspiratory flow (PNIF) were made over 60 min after each challenge. The primary end-point was the provocative concentration of AMP or allergen causing a 20% drop in the PNIF (PC_{20}).

Number of patients planned
30 patients recruited to complete 16 subjects

Number of patients analysed
16

Diagnosis and main criteria for inclusion
Male and female patients, aged 16–75, with intermittent and persistent allergic rhinitis, skin prick sensitization to a panel of seasonal and perennial aeroallergens, nasal hyper-responsiveness to AMP (>20% fall with incremental dose challenge), and FEV_1 >60% predicted (if they had concomitant asthma).

Test product dose

Arm A
Levocetirizine 5 mg

Arm B
Placebo

Duration of treatment
4 weeks (single dose of 5 mg levocetirizine/placebo administered 12 hours before the appointment on 4 separate occasions)

Reference therapy
None

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Primary Endpoint
Provocative concentration of AMP or allergen causing a 20% drop in the PNIF (PC_{20}).

Secondary Endpoints
Area under the 60 min time–response curve (AUC)

Statistical methods
The study was powered at 80% with an α-error of 0.05 (two-tailed) in order to detect a one-doubling dilution difference in the AMP PC_{20} threshold between randomized treatments, with an estimated sample size of 16 completed patients in a cross-over design. We also calculated the area under the 60 min time–response curve (AUC) as a secondary outcome. Lastly, a correlation and agreement analysis was performed between the allergen and AMP NPT. Each outcome was assessed for normality using the Kolmogorov–Smirnov test and by visual inspection of histograms and Q–Q distribution plots, with consideration of previous datasets and literature. PC_{20} values were not normally distributed and were logarithmically transformed. Paired Student's t-tests were applied to determine differences between treatment groups which were expressed as doubling dilution shifts. The AUC for recovery time-profile was distributed normally, so parametric tests were used. A mixed model analysis of variance (ANOVA) with Bonferroni's multiple-range testing [set at 95% confidence interval (CI)] to obviate multiple pair-wise comparisons was applied to compare serial time profiles for PNIF change from starting point of recovery (defined as the PNIF value at 20% drop from post-diluent measurement). PNIF percentage change was entered as a repeated measures variable, with treatment, sequence and rhinitis type as between-subject factors. We conducted a sequence analysis using the order of treatment (active vs. placebo) as a between-group variable in the ANOVA model, to account for individual variation across seasons. Agreement between the AMP and allergen challenge models for all outcome measures was quantified by plotting Bland–Altman plots. We calculated the within subject correlation coefficient by using multiple linear regression with subjects as categorical predictors. Analyses were performed using SPSS for Windows (v.14) Copyright 2006; SPSS Inc., Chicago, IL, USA.

Results
Ten women and six men with mean (SD) age of 51 (11) and 44 (17) years, respectively, completed protocol. The time-profile for PNIF recovery [area under the 60 min time–response curve as % PNIF change (min)] were significantly attenuated for AMP challenge, as mean difference [95% confidence interval (CI)]: 11.57 (3.87, 19.25), P = 0.005 and for allergen challenge: 17.82 (0.11, 35.53), P = 0.04. A highly significant correlation was shown between methods for the area under the curve: (R = 0.86, P<0.001). A statistically significant correlation was also seen for the PC20: (R = 0.94, P<0.001). PC_{20} improvement amounted to a 1.26 (95% CI 0.16, 2.35) and 0.16 (95% CI - 0.41, 0.73) doubling-dilution shifts for allergen and AMP challenges, respectively. Bland–Altman plots confirmed good agreement between methods.

Conclusion
A high correlation and statistical agreement has been demonstrated between AMP and allergen challenge for all outcome measures. In particular, the recovery profile after NPT is a sensitive and discriminatory measures of anti-allergic treatment.

Date of the report: 17.06.2016