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Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis

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Summary

Background Addition of H_1 antagonists to intranasal corticosteroid treatment of allergic rhinitis (AR) is common in clinical practice and recommended by guidelines, despite some evidence that the additive benefits are negligible.

Objective To assess additional benefits of 5 mg levocetirizine dihydrochloride in seasonal AR patients using 200 mcg fluticasone propionate nasal spray once daily.

Methods In a double-blind placebo-controlled crossover study of 27 patients, following 2 weeks without treatment, subjects used fluticasone with levocetirizine or identical placebo for 2 weeks each. Assessments were the Juniper mini Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ), domiciliary peak nasal inspiratory flow (PNIF), total nasal symptoms (TNS) scores and nasal nitric oxide concentrations. Effects were interpreted and tested against minimal clinically important differences.

Results Add-on effects for levocetirizine vs. placebo excluded any clinically significant benefits: mean effects (one sided 95% confidence intervals) were mini-RQLQ −0.11 (−0.34), PNIF +0.57 (+5.23), and TNS −0.11 (−0.60). Numbers needed to treat (95% confidence intervals) by outcome were mini-RQLQ 14 (5 to 49), PNIF 4 (3–7), and TNS 3 (2–6). No significant within or between treatment effects were seen for nasal nitric oxide.

Conclusion Contrary to current practice, the present results demonstrate that for the majority of patients, antihistamine add-on to effective nasal steroid treatment is inappropriate. Further work is required to confirm that this is also true in the most severe cases, and the available evidence needs to be put into guidelines and implemented.

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Introduction

Both antihistamines and nasal steroids are commonly used in the treatment of allergic rhinitis (AR). There is good evidence of efficacy for monotherapy with either, but the response is frequently incomplete and patient satisfaction is poor, so combination therapy is often started. The ARIA guidelines [1] comment 'The treatment of allergic rhinitis implies symptom reduction by drugs and attempts to interfere in the inflammatory cascade by anti-inflammatory drugs or specific immunotherapy ... theoretically, combining interventions at different levels should improve the clinical outcome'. The same report described differential effects for intranasal corticosteroids and antihistamines on symptoms, so it would seem intuitive that additive effects could exist.

A literature search (Medline, Cochrane, Embase and ancestor references) was conducted for evidence supporting add-on of antihistamines for patients using topical nasal steroids in AR.

In a recent review, Akerlund et al. [2] highlighted the lack of evidence to support newer guidelines that recommend the add-on of antihistamine to nasal steroid therapy.

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A review by Howarth [3] observed that there was no evidence from 'limited studies available' to support superiority of combination therapy compared with topical corticosteroid alone.

Ratner et al. [4] evaluated 2 week treatments with loratadine (10 mg once daily) and nasal fluticasone (200 mcg once daily) alone or in combination in moderate to severe seasonal AR and found no evidence of 'meaningful' additional benefits on symptoms scores and quality of life.

Di Lorenzo et al. [5] compared the use of nasal fluticasone (200 mcg once daily) alone and in combination with cetirizine (10 mg once daily) in moderate to severe seasonal AR, showing that combination therapy resulted in a statistically significant but small improvement in nasal itching and combined symptom scores. No significant improvements were seen for congestion, rhinorrhoea, sneezing, or percentage of eosinophils and eosinophil cationic protein in nasal washings.

Notably, none of the studies identified in our search conducted equivalence or non-superiority analyses comparing effects to defined limits of clinical relevance, and so were not able to conclude that combination therapy is clinically inappropriate.

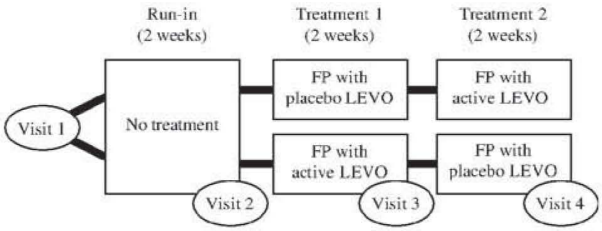
Combination therapy is certainly more expensive, and has the inherent risks of polypharmacy, including poor compliance, interactions and additional side-effects, which although rare and usually mild, do include sedation, palpitations, arrhythmias and hypersensitivity reactions.

We therefore conducted a double-blind placebo-controlled crossover study of the effects of fluticasone propionate alone or in combination with levocetirizine. Outcome assessments included both objective and subjective measures. The primary outcome was the Juniper mini-RQLQ [6]. We conducted a non-superiority analysis for levocetirizine vs. placebo as add-on to fluticasone treatment, with reference to minimal clinically important differences (MCIDs) for each outcome.

Methods

Patients

Participants were identified from our own database of patients in the Dundee area, Scotland. Inclusion criteria were male or female patients, aged 16–75 years, with seasonal (intermittent or persistent) AR, and skin prick-positive responses to grass pollen. Exclusion criteria were any other conditions affecting nasal airway patency, including septal deviation greater than 50%, and grade 2 polyps (extending below the upper edge of the inferior turbinate), pregnancy, lactation or any medical condition or screening blood result that might compromise participant safety.



Treatments, all taken in the morning:
FP (Fluticasone nasal spray) – two sprays to each nostril (200 mcg total).
LEVO (Levocetirizine tablets) – 5 mg.

Fig. 1. Study flow diagram.

Study design

The study (see Fig. 1) was conducted in four visits to the research laboratory in the months of June and July 2004 – the Dundee peak grass pollen season. All participants gave informed consent, and the protocol was given a favourable opinion by the multi-centre research ethics committee for Scotland.

Visit one (screening) determined inclusion and exclusion status. A medical history was taken, and routine blood tests (full blood count, urea and electrolytes, and liver function tests), nasal endoscopy and skin prick tests to common aeroallergens were performed (including mixed grass, positive and negative controls). Participants stopped any usual therapy with decongestants, antihistamines, anti-leukotrienes and nasal steroids, and were given sodium cromoglicate nasal spray and eye drops as rescue medication. Use of rescue medication was avoided for 24 h before each visit.

Participants attended visit 2 after 2 weeks without their usual treatments to establish baseline measurements.

For the remainder of the study, they took two sprays each side (200 mcg total) every morning of fluticasone nasal spray and either placebo or 5 mg levocetirizine tablets. An independent pharmacy encapsulated both tablets in an identical manner to blind the study. Fluticasone and levocetirizine doses were chosen to represent routine clinical practice. A crossover design was used; so all subjects received 2 weeks of combination therapy with fluticasone and levocetirizine and 2 weeks of monotherapy with fluticasone (and placebo) in a randomized order. Visit 3 was conducted after the first treatment and visit 4 after the second.

Measurements

All outcomes were measured or calculated for baseline (visit 2) and after each treatment period (visits 3 and 4).

Juniper mini Rhinoconjunctivitis Quality-of-Life Questionnaire. The mini-RQLQ [6] is a validated shortened version of the Juniper rhinoconjunctivitis quality-of-life questionnaire [7]. There are 14 questions in five domains

(activities, practical problems, nose, eye and other symptoms). Each question is scored for the preceding week as an integer from 0 (not troubled) to 6 (extremely troubled). The global mini-RQLQ score is the average (mean) of all question scores.

Domiciliary morning peak nasal inspiratory flow rate. PNIF measurements were noted each morning in a subject diary – each taken as the best of three from an In-Check® PNIF meter (Clement Clarke International Ltd, Harlow, UK). This is analogous to a reversed peak flow meter connected to a face mask to establish the maximal airflow rates on forced nasal inspiration. Subjects were instructed in the correct method, and the technique was assessed at screening, to ensure a seated posture, horizontal positioning of the meter, correct restoration of the reading to zero, a closed mouth, and an adequate mask seal while making a maximal nasal inspiration.

Domiciliary morning total nasal symptoms score. TNS scores were also recorded in the diary each morning. The TNS score is the sum of scores for nasal run, blockage, itch and sneeze, each measured on an interval scale of 0, 1, 2 or 3 representing no symptoms, mild, moderate or severe symptoms, respectively. This results in an integer score for TNS of 0 to 12.

Nasal nitric oxide levels. Nitric oxide levels are an objective marker of airway eosinophilic inflammation [8]. A Niox® nitric oxide analyzer (© 2000 Aerocrine AB, Solna, Sweden) was used at each visit to sample nitric oxide levels, using a method consistent with the joint statement [9] of the American Thoracic Society and the European Respiratory Society.

Statistical analysis and data presentation

The study was powered (at $> 90\%$) to detect ($P < 0.05$) a 0.7 U change (the MCID) in the primary outcome variable – the mini-RQLQ. The within subject standard deviation used was 0.32, as calculated in the instrument's initial validation [6]. Analyses were performed using Minitab, Copyright © 2004, Minitab Inc. PA, USA and SPSS for Windows (v11) Copyright © 2004, SPSS Inc. Chicago, IL, USA.

Each outcome was assessed for normality using Shapiro–Wilk tests and by eye, with consideration of previous data sets and the literature. All outcomes were considered normally distributed.

For PNIF and TNS, analysis was conducted on mean measurements for the final week of each period (treatment or run-in); for all other outcomes single (visit based) measurements were used.

Before non-superiority testing, differences within group (vs. baseline) were tested to demonstrate efficacy for all outcomes (null hypothesis – in the wider population no treatment effect exists). Non-superiority testing was then conducted for levocetirizine vs. placebo add-on therapy (null hypothesis – in the wider population the additional benefit of levocetirizine treatment vs. placebo is greater than the MCID).

Confidence intervals were calculated for both these comparisons – two-sided 95% confidence intervals for efficacy and one-sided 95% confidence intervals for non-superiority.

Finally, the number needed to treat (NNT) for one subject to experience a benefit greater than the MCID for each outcome was calculated.

Minimal clinically important difference determination

The MCID for the mini-RQLQ (± 0.7 U) was determined in its development by an anchor-based approach. MCIDs for PNIF (± 6.23), TNS (± 0.52) and nasal nitric oxide (± 68.7) were calculated using a distribution-based approach – each MCID is one-fifth of the outcome's standard deviation at baseline (see Table 3). Anchor- and distribution-based approaches are described in the discussion.

Data presentation

A summary by treatment period for each measurement taken is given in Table 2. Treatment effects for all outcomes (Table 3) were plotted (Fig. 3) using a scale on which +1 U represents an improvement of one MCID, thus enabling different outcomes to be plotted together and interpretations to be made of the statistical and clinical significance of treatment effects within and between groups. The plots also allow a comparison of the strength of signal and noise for all outcomes used. Interpretation of these plots is described in the discussion and in Fig. 5.

Results

Patient demographics (see Table 1)

Thirty-one subjects were initially enrolled for the study. Four subjects chose to withdraw for personal reasons. Eleven men and 16 women with mean (SD) age of 45.9 (15.0) and 44.2 (15.9) years respectively completed per protocol. Sixteen subjects received fluticasone with levocetirizine (combination) followed by fluticasone with placebo (monotherapy), 11 the opposite. Adverse events were recorded as (by treatment period) 1 × minor epistaxis (during combination therapy), 1 × URTI and 1 × lethargy (during monotherapy). No serious adverse events occurred.

Table 1. Demographics

Participant	Age	Sex	Sensitivities	Mini-RQLQ	FEV_1% Predicted
1	31	F	GHC	4.21	–
2	63	M	GH	1.64	–
3	55	F	G	1.93	–
4	37	M	GTW	1.50	–
5	48	M	GWHAF	4.86	–
6	55	M	GH	1.79	91
7	33	F	GC	2.07	–
8	28	M	GTWHDC	2.79	–
9	66	M	GWHAF	2.54	–
10	47	F	GTC	1.07	–
11	60	F	GH	3.07	–
12	32	M	GTW	1.43	–
13	57	F	GWA	1.86	–
14	58	F	GWH	2.29	–
15	65	F	GH	3.14	–
16	23	F	GWHC	3.50	–
17	61	F	GWH	1.50	–
18	60	M	GHC	1.57	–
19	30	M	GTWHCD	2.50	–
20	29	M	GTWHF	3.36	87
21	44	F	GDC	1.71	–
22	49	M	GW	3.00	–
23	18	F	GW	2.43	–
24	25	F	GWHC	4.29	–
25	49	F	GTWHAFDC	5.64	–
26	54	F	GHC	2.71	96
27	27	F	GTWHAFDC	1.43	90
28	18	F	GHC	2.21	–
29	21	F	GTW	4.71	101
30	57	M	GTW	4.86	–
31	39	F	GWHC	2.71	–

Sensitivities represent: G, grasses; T, trees; W, weeds; H, house dust mite; A, aspergillus; F, feathers mix; D, dog; C, cat. Mini Rhinoconjunctivitis Quality-of-Life Questionnaire (mini-RQLQ) is the score recorded at screening. Percentage predicted FEV_1 was only recorded for asthmatics.

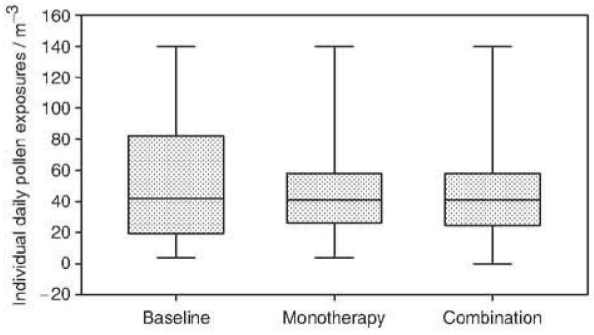


Fig. 2. Pollen exposures by treatment period. Boxplots -boxes show 2nd and 3rd quartiles, whiskers show minima and maxima.

Pollen Exposure (see Fig. 2)

Dundee pollen profiles have been published in this journal previously [10–12]. The 2004 pollen counts (52 m^{-3}, SEM 3.6) were not significantly different to previous years ($P = 0.67$). Individual daily pollen exposure is presented by treatment period in Fig. 2.

Table 2. Means (and standard errors) for all outcomes at baseline and following each randomised treatment

Outcome (units)	Baseline	Monotherapy	Combination
Mini-RQLQ (units)	2.5 (0.22)	1.7 (0.25)	1.6 (0.24)
PNIF (L/min)	118 (5.8)	130 (5.7)	131 (6.3)
TNS (units)	4.7 (0.46)	2.6 (0.51)	2.5 (0.53)
Nasal NO (ppb)	810 (64)	763 (77)	758 (67)

Mini-RQLQ, mini Rhinoconjunctivitis Quality-of-Life Questionnaire; PNIF, peak nasal inspiratory flow; TNS, total nasal symptoms score; NO, nitric oxide.

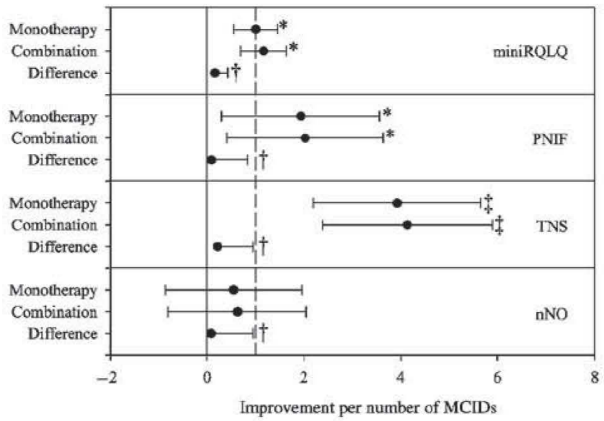


Fig. 3. Outcome improvements for each randomized treatment and differences between treatments. Results for monotherapy (fluticasone and placebo), combination (fluticasone and levocetirizine) and differences (add-on benefits) are plotted on a scale to depict changes relative to minimal clinically important differences (MCIDs). For within treatment effects two-sided 95% CIs are shown: ‡denotes statistically and clinically significant improvements. *denotes statistically significant improvements of uncertain clinical significance. For between treatment differences the one-sided 95% CIs are shown: †denotes non-superiority of combination therapy.

Within- and between-treatment effects (see Tables 2-4, Fig. 3)

Juniper mini rhinoconjunctivitis quality-of-life questionnaire. Statistically significant improvements were seen for change from baseline for both monotherapy ($P < 0.0001$) and combination therapy ($P < 0.0001$). The mean (one-sided 95% CI) for the difference between combination and monotherapy (i.e. levocetirizine add-on effects) was −0.11 (to −0.30), which excludes any benefit greater than the MCID, so we can dismiss the null hypothesis and conclude non-superiority: in the wider population, when used as add-on to fluticasone nasal spray, the

Table 3. Baseline data, MCID calculations and change by treatment group for all outcomes

Outcome (U)	Baseline Mean (95% CI)	SD at baseline	MCID (SD/5)	Monotherapy	Combination therapy	LEVO add-on effect
MiniRQLQ (U)	2.46 (2.03 to 2.90)	1.17†	0.7†	−0.70 (−1.02 to −0.39), $P < 0.0001$	−0.82 (−1.15 to −0.49), $P < 0.0001$	−0.11 (to −0.30), $P < 0.0001$
PNIF (L/min)	118 (107 to 130)	31.2	6.23	12.0 (1.9 to 22.2), $P < 0.05$	12.6 (2.6 to 22.6), $P < 0.05$	0.57 (to 5.23), $P < 0.05$
TNS (U)*	4.56 (3.61 to 5.50)	2.58	0.52	−2.02 (−2.91 to −1.13), $P < 0.0001$	−2.13 (−3.04 to −1.23), $P < 0.0001$	−0.11 (to −0.51), $P < 0.05$
nNO (ppb)	810 (682 to 938)	344	68.7	−37.4 (−134.5 to 59.6), $P = 0.44$	−43.1 (−142 to 55), $P = 0.37$	−5.6 (to −65.3), $P < 0.05$

Effect data are presented as means (95% confidence intervals) and *P*-values. *P*-values are the probability of non-efficacy vs. baseline except for add-on effects where *P*-values are the probability of superiority for combination therapy of 1 minimal clinically important difference or more.

*Individual symptom score data are presented in Table 4.

†Calculated in the instruments development.

LEVO, 5 mg daily Levocetirizine Dihydrochloride; Mini-RQLQ, mini Rhinoconjunctivitis Quality-of-Life Questionnaire; MCID, minimal clinically important difference; PNIF, peak nasal inspiratory flow; TNS, total nasal symptoms score; NO, nitric oxide.

additional mini-RQLQ benefit of levocetirizine treatment vs. placebo is not clinically important. Of 27 subjects, two experienced a benefit with levocetirizine add-on that was greater than the MCID – NNT 14 (95% CI 5–49).

Domiciliary morning peak nasal inspiratory flow rate. Statistically significant improvements were seen for change from baseline for monotherapy ($P < 0.05$) and combination therapy ($P < 0.05$). The mean (one-sided 95% CI) for the difference between combination therapy and monotherapy (i.e. levocetirizine add-on effects) was 0.57 (5.23), which excludes any benefit greater than the MCID, so we can dismiss the null hypothesis and conclude non-superiority: in the wider population, when used as add-on to fluticasone nasal spray, the additional PNIF benefit of levocetirizine treatment vs. placebo is not clinically important. Of 27 subjects, eight experienced a benefit with levocetirizine add-on greater than the MCID: i.e. NNT 4 (95% CI 3 to 7).

Domiciliary morning Total Nasal Symptoms score. Statistically significant improvements were seen for change from baseline for monotherapy ($P < 0.0001$) and combination therapy ($P < 0.0001$). The mean (one-sided 95% CI) for the difference between combination therapy and monotherapy (i.e. levocetirizine add-on effects) was −0.11 (−0.51), which excludes any benefit greater than the MCID, so we can dismiss the null hypothesis and conclude non-superiority: in the wider population, when used as add-on to fluticasone nasal spray, the additional TNS benefit of levocetirizine treatment vs. placebo is not clinically important. Of 27 subjects, nine experienced a benefit with levocetirizine add-on greater than the MCID: i.e. NNT 3 (95% CI 2–6). A breakdown by individual symptom scores is given in Table 4.

Nasal nitric oxide levels. No statistically significant improvements were seen for change from baseline for monotherapy ($P = 0.44$) or combination therapy ($P = 0.37$). Thus, we were unable to demonstrate a signal for nasal nitric oxide measurements at all, so no further conclusion should be drawn.

Sequence analysis

A comparison of randomization groups showed no statistically significant differences for carry-over ($P = 0.58$) or period ($P = 0.29$) effects on the primary outcome.

Discussion

In the present study, we set out to determine whether combination therapy with nasal fluticasone and oral levocetirizine was any more effective than fluticasone monotherapy. In view of the previous evidence, instead of hypothesizing a difference, we set out with the hypothesis that monotherapy could be considered no worse than combination therapy, i.e. non-inferior.

In AR, it is important to measure outcomes not only related to nasal airflow obstruction (PNIF, acoustic rhinometry or rhinomanometry), but also symptoms such as blockage, rhinorrhoea, itch and sneeze and the effects on global quality of life [13].

Both the mini-RQLQ and RQLQ have strong discriminative and evaluative measurement properties (defined by Guyatt et al. [14]), and the mini-RQLQ is significantly more responsive than the earlier rhinoconjunctivitis quality-of-life questionnaire [6, 7].

We have previously shown that PNIF is a representative and repeatable (cv. 8%) [15] measure of nasal airflow obstruction, and that it is more sensitive than acoustic rhinometry for monitoring response to histamine nasal challenges [16]. Nasal nitric oxide is considered a reproducible (cv. 13% [17]), non-invasive and easily obtained nasal inflammatory marker.

For our drug interventions we chose to study levocetirizine add-on to fluticasone nasal spray over a 2-week period to represent the current best treatment. Fluticasone is among the most commonly used of the nasal steroids available in our rhinology clinic, and has a high

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