

# A Randomized Controlled Trial of Cetirizine Plus Pseudoephedrine Versus Loratadine Plus Pseudoephedrine for Perennial Allergic Rhinitis

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**SUMMARY** The purpose of this study was to compare the safety and efficacy of cetirizine plus pseudoephedrine (C+P) with loratadine plus pseudoephedrine (L+P) in the treatment of perennial allergic rhinitis. This was a double blind, randomized, parallel trial with an active control. Subjects aged 12 to 70 years with perennial allergic rhinitis for at least 2 years were enrolled and randomized to receive either of the active study medications plus a placebo resembling the other, twice daily for 4 weeks. Nasal total symptom scale (NTSS) including sneezing, rhinorrhea, nasal itching and nasal stuffiness is evaluated by subjects daily and at baseline, 2 weeks, and 4 weeks by the investigator as efficacy measurement. A total of 51 eligible patients were enrolled and 45 patients completed the treatment course. Both groups had significant reductions in NTSS after 4 weeks of treatment as assessed by the subjects, but there was no significant difference between the two groups (mean  $\pm$  SD) reduction of  $4.25 \pm 2.45$  with C+P vs.  $3.52 \pm 2.41$  with L+P,  $p = 0.215$ . As assessed by the investigator, sneezing was significantly better at 2 weeks ( $-1.13$  vs.  $-0.52$ ,  $p = 0.028$ ) and nasal congestion at 4 weeks ( $-1.71$  vs.  $-1.19$ ,  $p = 0.031$ ) in subjects treated with C+P compared to those treated with L+P. There were 37 treatment-related adverse events (5 in 4 subjects in the C+P group and 32 in 16 subjects in the L+P group). It was concluded that both cetirizine plus pseudoephedrine and loratadine plus pseudoephedrine are efficacious for perennial allergic rhinitis in Taiwanese subjects. Relief of sneezing and nasal congestion may be marginally better with the cetirizine preparation, which also seemed to be slightly better tolerated, although the incidence of side effects did not differ significantly.

Allergic rhinitis is symptomatic disorder of the nose induced by IgE-mediated inflammation after the nasal membrane is exposed to an allergen. The symptoms include nasal congestion, rhinorrhea, sneezing, and nasal pruritus. In addition, patients may also experience ocular pruritus, paranasal pain, headache, anosmia, dysosmia, chronic pharyngitis, and recurrent infections of the nose or sinuses.<sup>1</sup> An increasing prevalence of allergic rhinitis over the last decades has been recognized in several countries,<sup>2-4</sup> a

trend seen in Taiwan as well, with a yearly increase from 7.84% in 1985 to 33.53% in 1994.<sup>5-7</sup> The disorder, which may be seasonal or perennial, causes major discomfort of those affected and may seriously

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impair work and school performance and the quality of sleep, in some cases even leading to psychological disturbance.<sup>8-10</sup> Thus, treatment for allergic rhinitis is an important health care issue.

First-line treatment consists of oral antihistamines in conjunction with allergen avoidance.<sup>11</sup> The second-generation non-sedating antihistamines are particularly useful. Cetirizine and loratadine are both potent second-generation H1-antagonists that are not associated with the adverse central nervous system and anticholinergic effects seen with first-generation agents. Both agents are efficacious and well tolerated in the treatment of allergic rhinitis in adults and children.<sup>12-17</sup>

However, while these agents suppress histamine-mediated symptoms such as sneezing and nasal discharge, they are generally not effective in relieving symptoms of nasal congestion, a phenomenon driven by a number of vasoactive mediators in addition to histamine.<sup>18,19</sup> For this reason, antihistamines are often prescribed in combination with decongestants, which act to constrict the blood vessels in the mucous membranes and thus diminish nasal congestion. One such decongestant is pseudoephedrine, a sympathomimetic drug that acts directly on adrenergic receptors in the respiratory tract mucosa to cause vasoconstriction, resulting in shrinkage of swollen nasal mucous membranes; reduction in nasal congestion and increased nasal patency and sinus drainage.<sup>20</sup>

The clinical benefits of antihistamine-decongestant combination products are well established, and a number of such products are available by prescription or over the counter. Previous studies have shown cetirizine plus sustained-release pseudoephedrine is more effective than either drug given alone for overall relief of the symptoms of allergic rhinitis.<sup>21,22</sup> A similar result is seen with loratadine plus pseudoephedrine,<sup>23</sup> but these two antihistamine-decongestant combinations have not been directly compared in a head-to-head study. The purpose of this study was to compare the efficacy and safety of cetirizine plus pseudoephedrine with that of loratadine plus pseudoephedrine in Taiwanese adolescents and adults with perennial allergic rhinitis.

## MATERIALS AND METHODS

Subjects aged 12 to 70 years old in Taiwan with allergic rhinitis for at least 2 years were enrolled in this double-blind, double dummy, randomized, parallel, actively controlled trial carried out from September to November 2004. Allergic hypersensitivity was confirmed by positive specific IgE result ( $\geq$  class 2) within the past year.

Patients were excluded from the study for the following reasons: pregnancy or lactation, undergoing desensitization therapy, a history of hypersensitivity to the use of cetirizine, loratadine, pseudoephedrine or adrenergic agents. Also excluded were patients with severe persistent asthma.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and/or the local laws and regulations. The current guidelines for Good Clinical Practice (Taiwan- and ICH-GCP guidelines) were also applied. The study protocol and informed consent form were forwarded to the Institutional Review Board (IRB) of Mackay memorial hospital as well as the health authorities for review and approval prior to the beginning of the study. All patients (or their parents or legal representatives if aged less than 18 years) gave written informed consent to participate this study.

Subjects were required to avoid parental, oral or nasal corticosteroids within 30 days, loratadine; cetirizine, antileukotrienes for 7 days; and other H1 antihistamine and nasal decongestant for 3 days.

All eligible subjects were randomized to one of the two treatment groups in 1:1 ratio. Active treatment consisted of either cetirizine 5 mg and sustained-release pseudoephedrine 120 mg (C+P) or loratadine 5 mg and sustained-release pseudoephedrine 120 mg (L+P). Subjects in each group also received a placebo resembling the other active treatment. The medication was to be taken twice daily for 28 days. Patients were scheduled to be seen four times during the trial, including a screening visit, randomization visit, evaluation visit and final visit, as shown in Fig. 1.

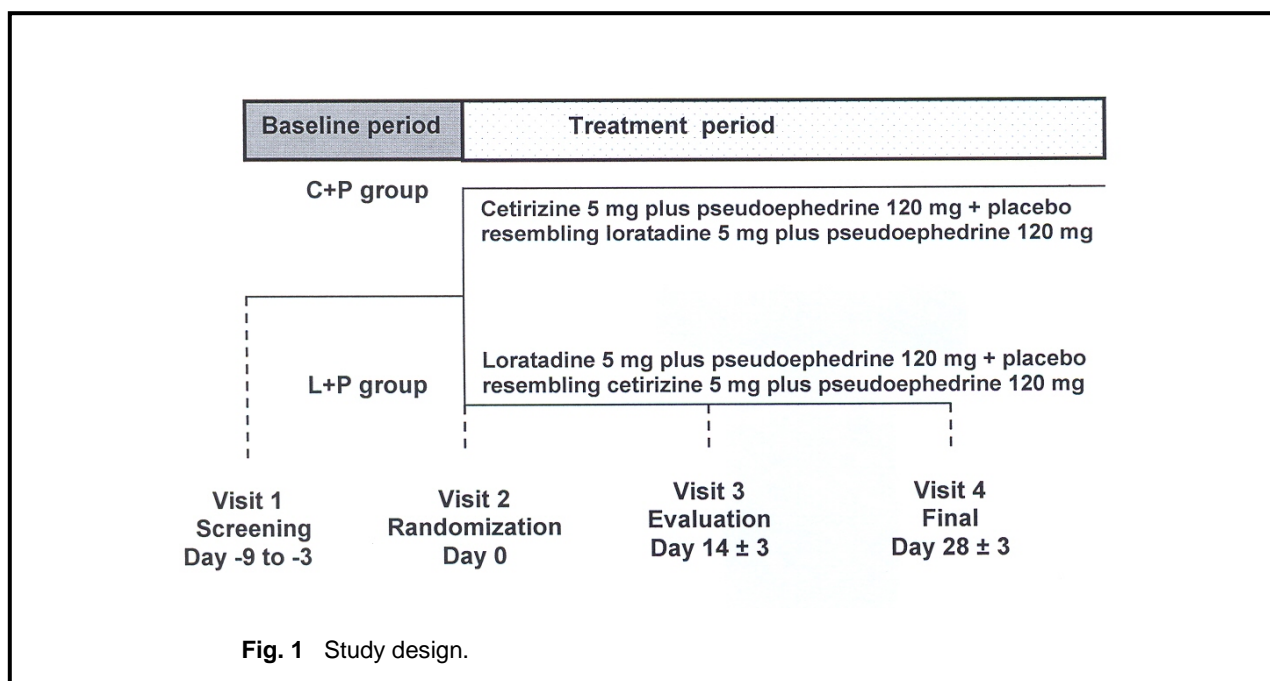


Fig. 1 Study design.

Table 1 Demographic and baseline characteristics

Characteristics	C+P (N = 25)	L+P (N = 26)	p-value
Age (years)*	28.88 (9.31)	28.15 (9.06)	0.877 <sup>a</sup>
Weight (kg)*	64.04 (15.57)	63.88 (12.84)	0.969 <sup>b</sup>
Height (cm)*	168.36 (8.36)	164.83 (8.23)	0.163 <sup>a</sup>
BMI (kg/m <sup>2</sup> )*	22.46 (4.66)	23.39 (3.46)	0.203 <sup>a</sup>
Gender (male/female)	13/12	13/13	1.000 <sup>c</sup>
Compliance (%)*	92.14 (7.23)	93.51(20.10)	0.970 <sup>a</sup>
NTSS by subjects*	7.79 (1.19)	8.11 (1.53)	0.405 <sup>b</sup>
NTSS by investigators*	8.56 (1.89)	8.42 (1.36)	0.768 <sup>b</sup>

a: Wilcoxon ranked-sum test; b: Two sample t-test; c: Fisher's exact test, \*Mean (SD)

The evaluation of efficacy was based on the following allergic symptoms, including sneezing, rhinorrhea, nasal itching, and nasal stuffiness. The severity of each symptom was using a four-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Scores for each symptom were added to obtain a Nasal Total Symptom Score (NTSS). It was assessed daily by the subjects themselves and by the investigators at each visit.

To qualify for enrollment in the randomized treatment phase, the average daily nasal total symp-

tom scores throughout baseline period and the day before visit 2 must have been symptom scores of rhinorrhea  $\geq 1$ , nasal stuffiness  $\geq 2$ , sneezing  $\geq 1$  and sums of symptom scores of rhinorrhea, nasal stuffiness and sneezing  $\geq 5$ .

Subjects make a global assessment *via* 10-cm visual analogue scale (VAS) at the end of study. The VAS was a 10 cm horizontal line with the extreme left (0 cm) indicating no improvement and the extreme right (10 cm) indicating the greatest improvement.

Vital sign, physical examination and adverse events were assessed at each visit. Hematology and blood chemistries were assessed at screening visit and at the final visit.

Efficacy parameters were analyzed by analysis of covariance (ANCOVA). The incidence of adverse events was analyzed by Fisher's exact test. Data are presented as the mean  $\pm$  SD. Treatment effect variables are reported as a point estimate with a 95% confidence interval. Comparison tests are reported with a *p* value. Any *p* value  $< 0.05$  defined as statistical significance.

## RESULTS

From September to November 2004, 51 subjects were randomized into the study and a total of 45 patients completed the treatment course with 24 subjects in the C+P group and 21 subjects in the L+P group. The mean duration of allergic rhinitis since its onset was 15.8 years in C+P group and 15.9 years in L+P group. Demographic characteristics and baseline characteristics showed no statistical difference (Table 1), indicating the two groups were comparative at the start of the study.

A mean reduction in NTSS from baseline to the fourth week evaluated by subjects was  $4.25 \pm 2.45$  in the C+P group and  $3.43 \pm 2.52$  in the L+P group, as shown in Table 2. Both treatments were effective in reducing the mean NTSS at the end of the treatment period. However, the results for the two groups did not differ significantly ( $p = 0.215$ ).

As with the patients' assessment, the mean reduction in NTSS as assessed by the investigator

did not differ significantly between the two groups even though on cursory inspection it appears that C+P yielded slightly better results (Table 2). In each group, the treatment effect appeared stronger at week 4 than at week 2, but again, the differences were not statistically significant.

As assessed by the investigators, two of the individual symptom scores were significantly improved by C+P compared with L+P. Sneezing was better with C+P at week 2 (a reduction of 1.13 vs. 0.52,  $p = 0.028$ ) and nasal congestion at week 4 (a reduction of 1.71 vs. 1.19,  $p = 0.031$ ) (Fig. 2).

The mean improvement based on the VAS in the C+P group was  $5.55 \pm 1.92$  cm (95% CI 4.40 to 7.10) compared with 5.92 (95% CI 4.40 to 7.10), a nonsignificant difference ( $p = 0.453$ ). All subjects reported at least some improvement after 4 weeks of treatment, with a minimum score of 1.50 in the C+P group and 0.80 in the L+P group.

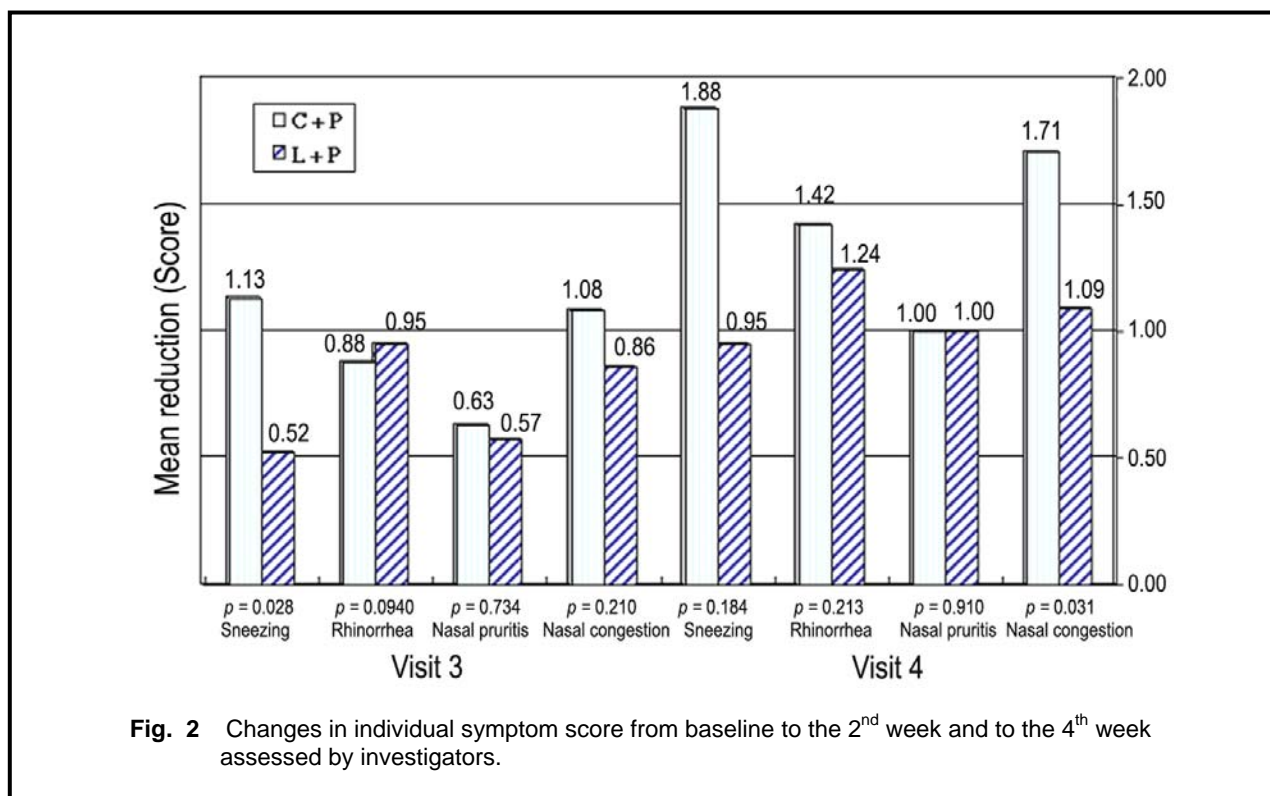
Four (of 25, 16%) of C+P-treated subjects versus 12 (of 26, 46%) L+P-treated subjects experienced at least one adverse event (Table 8). This difference was not statistically significant ( $p = 0.144$ ), although the relative risk of 0.320 appeared lower for the C+P group.

A total of 5 adverse events were recorded in the C+P group compared to 32 in the L+P group. The most frequently reported adverse effect in the C+P group was insomnia (7.4%). In the L+P group, the most common complaint was headache (19.2%), followed by pharyngitis in 15.4%, palpitations in 11.5%, increased cough increased in 11.5%, asthenia in 7.7%, and dizziness in 7.7%. One subject in the

**Table 2** Change in mean NTSS from baseline to the 2<sup>nd</sup> and 4<sup>th</sup> week as assessed by subjects and investigators

Statistics	C+P (N = 24)	L+P (N = 21)	Difference <sup>a</sup> (95%CI)	<i>p</i> -value <sup>b</sup>
2 <sup>nd</sup> week by subjects	-3.91 (2.11)	-3.57 (2.13)	0.48 (-0.70 to 1.65)	0.418
4 <sup>th</sup> week by subjects	-4.25 (2.45)	-3.43 (2.52)	0.914 (-0.55 to 2.38)	0.215
2 <sup>nd</sup> week by investigators	-3.71 (1.97)	-2.90 (1.61)	0.72 (-0.20 to 1.64)	0.121
4 <sup>th</sup> week by investigators	-5.50 (2.77)	-4.38 (2.52)	1.01 (-0.41 to 2.43)	0.157

a: C+P minus L+P; two-sided 95% CI of mean difference based on ANCOVA,  
b: ANCOVA with treatment effect and covariate of baseline,  
\*Mean (SD).



C+P group dropped out complaining of drug-related insomnia. Two in the L+P group dropped out, one complaining of moderately severe palpitations, dizziness, headache, weakness, and thirst and the other of skin rashes after drug intake. Overall, there were no serious adverse effects reported and there were no deaths.

## DISCUSSION

Our study demonstrates that both cetirizine and loratadine when combined with sustained-release pseudoephedrine significantly improve the symptoms of allergic rhinitis after 4 weeks of treatment. In terms of individual symptoms, investigators found better improvement in sneezing at 3 weeks and nasal congestion at 4 weeks in subjects treated with C+P. Cetirizine and loratadine have been directly compared in multicenter trials of pollen-induced allergic rhinitis and in an outdoor park study. In the latter, cetirizine had a more rapid onset of action and provided greater symptom relief than did loratadine.<sup>24</sup> The results of clinical trials comparing cetirizine with loratadine for allergic rhinitis have varied, with some studies showing greater improvement with cetirizine<sup>25-27</sup> but others demonstrating no

statistically significant difference.<sup>14,28,29</sup> The novel aspect of our study was direct comparison of the two agents each in combination with a decongestant. Both preparations significantly improved symptoms, but we were unable to demonstrate a clinically significant difference between the two, even though the cetirizine group seemed in general to score a slightly better than the loratadine group.

In the global assessment by the subjects, the efficacy of both preparations was confirmed. In terms of specific symptoms, nasal congestion was definitely improved by both agents, an effect not generally seen with antihistamines alone.

The incidence of adverse event in patient treatment with C+P was fewer than previous studies. Previous study have shown 29.6% subjects treated with C+P for 2 weeks had at least one adverse event in 230 patients<sup>22</sup>, and 50% subjects for 3 weeks in 70 patients.<sup>21</sup> In the present study only four (16.0%) C+P treated subjects were reported to experience at least one adverse event.

Both agents were generally well tolerated, although those in the C+P group reported fewer

adverse affects that those taking L+P. This was not a statistically significant difference, although that may be because the absolute number of subjects with adverse events was too small to demonstrate a true difference if one exists. Insomnia was the most frequently reported treatment-related adverse event in the C+P group, which may have been secondary to the pseudoephedrine. Headache was the most commonly recorded side effect in the L+P group as had been reported in other studies.<sup>23,30,31</sup> No death occurred, and there were no serious or unexpected adverse events reported that were attributable to either C+P or L+P therapy. Based on our study, in the short term, both these agents appear to be safe and well tolerated.

It was concluded from the clinical trial among Taiwanese subjects that both cetirizine plus sustained-release pseudoephedrine and loratadine plus sustained-release pseudoephedrine twice daily were efficacious in the treatment of perennial allergic rhinitis over at least 4 weeks. Relief of sneezing and nasal congestion may be better with the cetirizine preparation, which also seemed to be slightly better tolerated, although we could not demonstrate a significant difference in the incidence of side effects.

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