

# EFFICACY AND SAFETY OF LORATADINE COMPARED WITH ASTEMIZOLE IN MALAYSIAN PATIENTS WITH ALLERGIC RHINITIS

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## ABSTRACT

*Nonsedating selective peripheral H<sub>1</sub> receptor antagonists are an important advance in antihistaminic therapy in allergic patients. This is a randomised, double-blind parallel group study comparing the use of two such agents viz loratadine 10mg daily and astemizole 10mg daily for two weeks in 39 Malaysian allergic rhinitis patients. At these dosages, both drugs were demonstrated to be efficacious ( $p < 0.05$ ) for controlling nasal symptoms and safe in terms of short term biochemical and haematological changes and adverse effects noted. Evaluating efficacy criteria utilised in this study loratadine and astemizole were comparable but loratadine was significantly more effective in three areas viz: (i) in diminishing nasal symptoms after 2 weeks of treatment ( $p = 0.03$ ); (ii) physician's efficacy evaluation after 2 weeks' treatment ( $p = 0.009$ ); (iii) patient's efficacy evaluation after 2 weeks' treatment ( $p = 0.019$ ).*

**Keywords:** allergic rhinitis, antihistamines, loratadine, astemizole, randomised double-blind study

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## INTRODUCTION

Antihistaminic drugs were efficacious in the treatment of allergic disorders. The concomitant sedative effects of the antihistamines have been a limiting factor in their use in such affected patients<sup>(1)</sup>. This led to the development of the newer nonsedating selective peripheral H<sub>1</sub> receptor antagonists including loratadine, astemizole and terfenadine<sup>(2,3)</sup> which are all available in Malaysia and Singapore. Terfenadine is given on a twice daily dosage while loratadine and astemizole have the advantage of a single daily dosing pattern. Loratadine has been found comparable or superior in efficacy to terfenadine<sup>(4,5)</sup> and astemizole<sup>(6)</sup>. These are Western based studies with no reference to the Asian patient. This is the first and only study to date done in Malaysian allergic rhinitis patients with the objective of comparing the efficacy and safety profile of loratadine 10mg daily (OD), with that of astemizole 10mg daily (OD). It is a randomised double-blind, parallel group study of patients with moderate to severe allergic rhinitis with an emphasis on the results at the end of one and two weeks of treatment.

## METHODS

Patients presenting to the Allergy Clinic of the Otolaryngology Department of the University Hospital Kuala Lumpur who were clinically allergic with at least one positive skin prick test (with a wheal diameter 3mm or greater than that of control) were screened by the two investigators (authors).

Patients selected had to have:

- moderate to severe rhinitis as defined by at least two of the 4 nasal symptoms studied being moderate and combined severity of nasal symptoms plus eye itching totalling six. The nasal symptoms include nasal discharge, nasal stuffiness, nasal itch and sneezing.

|   |   |          |   |
|---|---|----------|---|
| 0 | = | None     | (No symptoms are evident)   |
| 1 | = | Mild     | (Symptoms do not interfere with daily activities and/or sleep)      |
| 2 | = | Moderate | (Some interference with daily activities and/or sleep)              |
| 3 | = | Severe   | (Significant/major interference with daily activities and/or sleep) |

Patients were excluded if they were pregnant, lactating or

- had a history of documented asthma or reversible bronchoconstriction within the previous 2 years,
- had received any immunotherapy with pollen extracts within 6 months prior to the study,
- had any significant concurrent disease,
- had a clinically significant abnormal laboratory test result,
- had a known idiosyncratic reaction to antihistamines, or a history of multiple drug allergies,
- had taken any investigational drugs within one month prior to the start of this study,
- had used any antihistamines, oral or topical decongestants within 24 hours of the first test dose,
- had taken corticosteroid preparations, either systemic or inhaled aerosol, or cromolyn sodium within two weeks of the first test done,
- or were known non-responders to antihistamine therapy.

Thirty-nine such patients were eventually enrolled in this double-blind study and randomly assigned to receive either loratadine 10mg OD (20 patients) or astemizole 10mg OD (19 patients) orally for a two-week period.

The study design required four visits at weekly intervals. Patients were supplied with diary cards to record symptoms of rhinitis daily and were assessed at Visit 1 (Day-7), Visit 2 (Day 0), Visit 3 (Day 7) and Visit 4 (Day 14). Day 0 indicates the day of starting drug and Day 14 indicates the fourteenth and last day of medication. Day-7 indicates the seventh day before starting medication intake. No antihistamines, corticosteroids, cromolyn or decongestants were allowed between Visits 1 and 2.

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Investigational drug therapy was initiated at Visit 2 and ended at Visit 4.

Efficacy was assessed by changes from baseline in symptom scores and by the physician's and patient's evaluation of therapeutic response after one and two weeks of treatment. This was rated as excellent (all symptoms have been eliminated), good (most symptoms are improved, but some symptoms are still listed as mild), fair (some response, but most symptoms are still present), poor (minimal response) and treatment failure (no change or worse than pre treatment baseline). Drop-outs were defined as those patients who had completed the first week of treatment but did not present for evaluation at end of the second week.

Four nasal and four non-nasal symptoms commonly associated with allergic rhinitis were evaluated. Nasal symptoms included discharge, stuffiness, itch and sneezing. Non-nasal symptoms included eye itch, eye watering, eye redness and itching ears or palate.

Symptom scores were recorded at all four visits.

Safety was evaluated by recording any adverse experiences noted. The investigator made a medical judgement on the relationship of any adverse experience to drug administration as probably, possibly or not related to therapy. Complete blood count and blood chemistry tests were undertaken at Visits 1 and 4.

This study received the permission of the Ethics Committee of the University Hospital Kuala Lumpur.

Several statistical analyses were used in calibrating the data. Treatment group comparisons between loratadine and astemizole were made for each of the 4 visits for the mean total nasal symptoms, mean total non-nasal symptoms and mean total nasal and non-nasal symptoms. This was evaluated by using the t-test.

For each of the 3 symptom groups viz mean total nasal symptoms, mean total non-nasal symptoms, and mean total nasal and non nasal symptoms, mean scores for all 39 patients were obtained for each of the 4 visits. A two-way analysis of variance test was performed for each symptom group to assess the change of mean symptom scores across visits 1 to 4.

T-test analysis comparing haematological and biochemical data before (Visit 1) and after treatment (Visit 4) for each drug was also performed.

P values less than 0.05 are taken as significant.

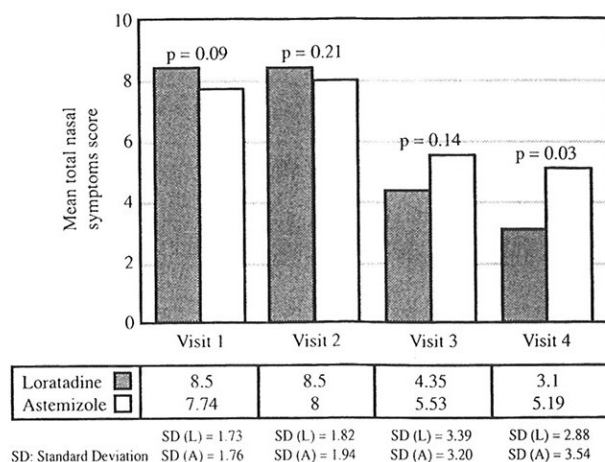
## RESULTS

The mean total nasal symptoms, mean total non-nasal symptoms and mean sum of total nasal and non-nasal symptom scores for loratadine versus astemizole are shown in Figs 1 to 3.

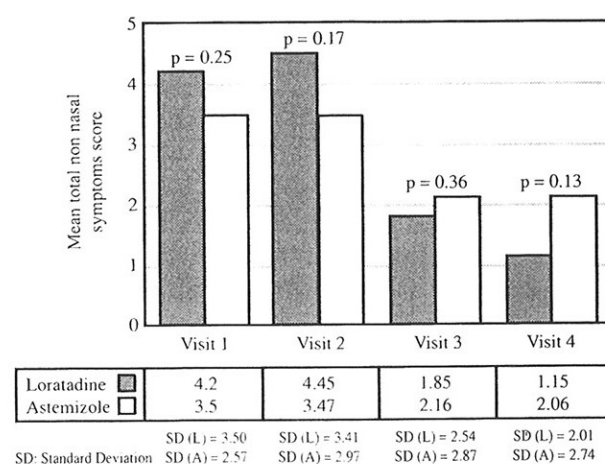
T-test analysis comparing loratadine and astemizole at each of the 4 visits was performed for each of the above 3 groups. The p value results are given in Figs 1 to 3. The only significant difference was for the loratadine and astemizole comparison for mean total nasal symptoms at Visit 4 ( $p = 0.03$ ). For total non-nasal symptoms and for mean sum of total nasal and total non-nasal symptoms, no significant values were obtained.

For the 2-way analysis test of change of mean symptom scores for all 39 patients across visits 1 to 4, significant results were found for the symptom groups mean total nasal symptom scores ( $p = 0.047$ ) and mean sum of total nasal and non-nasal symptom scores ( $p = 0.03$ ). There was no significant result for the symptom group mean total non-nasal symptoms ( $p = 0.06$ ). This is shown in Table I.

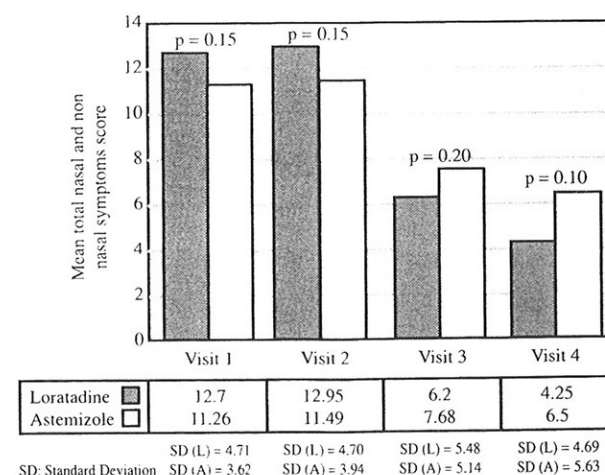
**Fig 1 – Mean total nasal symptoms of loratadine vs astemizole of each visit.**



**Fig 2 – Mean total non nasal symptoms of loratadine vs astemizole for each visit.**



**Fig 3 – Mean total nasal and non nasal symptoms of loratadine vs astemizole for each visit.**



**Table I – Mean scores for each symptom group across 4 visits**

|   | Visit 1 | Visit 2 | Visit 3 | Visit 4 | 2 way analysis of variance (p) |
|---|---------|---------|---------|---------|--------------------------------|
| Mean total nasal symptoms (n = 39)                      | 8.12    | 8.25    | 4.94    | 4.145   | 0.047                          |
| Mean total non-nasal symptoms (n = 39)                  | 3.865   | 3.96    | 2.005   | 1.605   | 0.062                          |
| Mean sum of total nasal and non-nasal symptoms (n = 39) | 11.98   | 12.21   | 6.94    | 5.375   | 0.03                           |

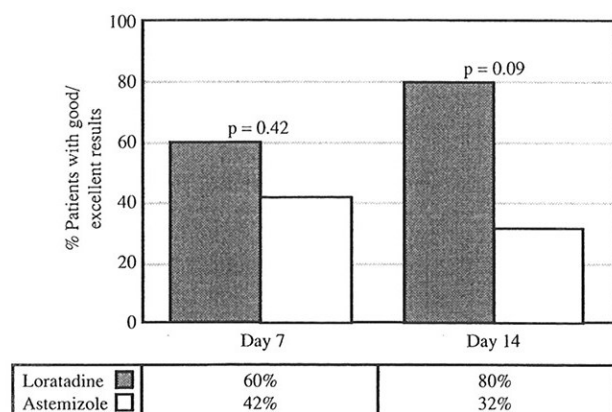
The physician's evaluation of therapeutic response is shown in Table II. Excellent or good response to treatment as assessed by the investigator is shown in Fig 4. This response was greater with loratadine than astemizole both at Day 7 and 14 with a significant difference at Day 14 ( $p = 0.009$ ) but not at Day 7 ( $p = 0.42$ ).

**Table II – Physician's evaluation of therapeutic response**

|             | Excellent | Good | Fair | Poor | Treatment | Drop Out |
|-------------|-----------|------|------|------|-----------|----------|
| Day 7       |           |      |      |      |           |          |
| Loratadine  | 3         | 9    | 5    | 3    | 0         | 0        |
| Astemizole* | 1         | 6    | 4    | 3    | 3         | 0        |
| Day 14      |           |      |      |      |           |          |
| Loratadine  | 5         | 11   | 1    | 3    | 0         | 0        |
| Astemizole  | 2         | 3    | 5    | 2    | 4         | 3        |

\*No record of 2 responses

**Fig 4 – Physician's evaluation of therapeutic response to loratadine and astemizole respectively after one and two weeks of treatment.**



The patient's evaluation of therapeutic response is shown in Table III. Excellent or good response to treatment as assessed by the patient is shown in Fig 5. This response was also greater with loratadine than astemizole both at Day 7 and 14 with a significant difference at Day 14 ( $p = 0.019$ ) but not at Day 7 ( $p = 0.42$ ).

There were no noteworthy adverse reactions recorded with both groups.

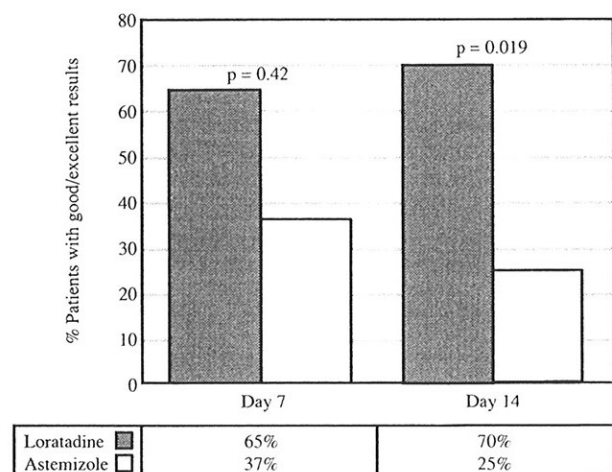
No statistically significant differences were found in comparing haematological and biomedical data before (Visit 1) and after treatment (Visit 4) for each drug respectively (Table IV).

**Table III – Patient's evaluation of therapeutic response**

|             | Excellent | Good | Fair | Poor | Treatment | Drop Out |
|-------------|-----------|------|------|------|-----------|----------|
| Day 7       |           |      |      |      |           |          |
| Loratadine  | 3         | 10   | 4    | 2    | 1         | 0        |
| Astemizole* | 1         | 6    | 3    | 4    | 4         | 0        |
| Day 14      |           |      |      |      |           |          |
| Loratadine  | 5         | 9    | 4    | 2    | 0         | 0        |
| Astemizole  | 2         | 2    | 5    | 3    | 4         | 3        |

\*No record of 1 response

**Fig 5 – Patient's evaluation of therapeutic response to loratadine and astemizole respectively after one and two weeks of treatment.**



**Table IV – T-test analysis of change in laboratory data before and after treatment for loratadine and astemizole respectively**

|                            | p values   |            |
|----------------------------|------------|------------|
|                            | Loratadine | Astemizole |
| Haemoglobin                | 0.93       | 0.67       |
| Haematocrit                | 0.30       | 0.83       |
| White blood cell count     | 0.80       | 0.95       |
| Creatinine                 | 0.97       | 0.18       |
| Alkaline phosphatase       | 0.45       | 0.85       |
| Aspartate aminotransferase | 0.62       | 0.81       |
| Alanine aminotransferase   | 0.97       | 0.90       |
| Bilirubin                  | 0.93       | 0.82       |

p values – Each value given represents the t-test analysis comparing each laboratory test result obtained before and after usage of loratadine or astemizole respectively. All the p values obtained were  $> 0.05$  indicating that neither drug caused any statistically significant change in laboratory data pre and post treatment.

## DISCUSSION

In considering efficacy of treatment of an investigational drug, it can be compared against a placebo or another biochemically active drug or both.

It is generally accepted and supported by previous clinical trials that antihistamines have an anti-allergic effect over and above that due to placebo alone<sup>(7,8)</sup>. Also previous trials where loratadine was compared with placebo had shown that loratadine

had significantly superior effect on allergic symptomatology<sup>(3,8,9)</sup>. It was thus felt that within the constraints of time and cost, loratadine would only be compared against another active antihistaminic drug but not including a placebo group. Astemizole, being also a member of the new class of non sedating antihistaminic drugs, was selected.

Randomisation procedure was used to obtain comparable groups. The non significant p value results obtained in the comparative t-test analysis of loratadine and astemizole at Visits 1 and 2 (pre treatment) for mean total nasal symptoms, mean total non-nasal symptoms and mean total nasal and non-nasal symptoms are further indications that the two groups are in fact comparable.

The comparative analysis between loratadine and astemizole in terms of effectiveness in reducing symptom scores brought to light that both drugs were comparable in all respects except that loratadine was giving superior results in diminishing nasal symptoms after 2 weeks of treatment ( $p = 0.03$ ).

In terms of changes in mean symptom scores across visits, it can be concluded that both loratadine and astemizole were effective in diminishing nasal symptoms ( $p = 0.047$ ) but had less effectiveness in affecting non-nasal symptoms ( $p = 0.06$ ).

Efficacy was also assessed by looking at therapeutic response as evaluated by the physician and patient separately. It was interesting that in both situations, loratadine was rated comparably to astemizole after one week of treatment but after 2 weeks of treatment, loratadine was rated superior both by the physician ( $p = 0.009$ ) and patient ( $p = 0.019$ ).

It is difficult to account for the last finding as it is known that astemizole has a long half life and should theoretically have an increasing cumulative effect over 2 weeks of treatment. It is postulated that perhaps drug tolerance to astemizole developed in this study group.

Not surprisingly, there were no noteworthy adverse reactions recorded. Similarly it is reassuring that for both drugs, there were no significant changes in haematological and biochemical values following the treatment. Both observations have to be assessed in the light that the duration of treatment was only 2 weeks and it should not be assumed that the same would necessarily hold

on long-term usage. Cardiac ventricular arrhythmias have been reported with astemizole but arising in the clinical situation of overdose<sup>(10,11)</sup>. To the authors' knowledge, there have been no similar reports with loratadine.

## CONCLUSION

This study demonstrates that both loratadine 10mg OD and astemizole 10mg OD are safe, well tolerated and effective in relieving signs and symptoms of allergic rhinitis. The efficacy of both drugs applies particularly to nasal related symptoms but less so to non-nasal symptoms. From symptom score assessment and from physician's and patient's evaluation, loratadine was comparable to astemizole in efficacy on all counts except after 2 weeks of treatment, where loratadine was superior to astemizole in treating nasal related symptoms.

Short term prescribing of both drugs is safe with no noteworthy adverse effects.

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