Modification of Antihistaminic Activity of Cetirizine by Nimesulide

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ABSTRACT

- **Objective :** To study the effect of nimesulide (4-nitro-2-phenoxymethane sulfonanilide) a non-steroidal anti-inflammatory drug, on antihistaminic activity of cetirizine.
- **Method :** A randomized, double blind, cross over study was conducted in ten healthy male volunteers. Wheal and flare responses to histamine were measured by performing intradermal injection of histamine (2 u.g base) diluted in 100 (J.I volume of saline on the volar surface of forearm, on four occasions (0, 2,4, and 6 hrs. post-dosing). Each volunteer was randomized to receive either treatment A (cetirizine 10 mg + placebo) or treatment B (cetirizine 100 mg + nimesulide 100 mg), with one week wash out period in between each administration. Wheal and flare responses were measured ten minutes after each histamine injection.
- **Results :** Both cetirizine 10 mg alone and cetirizine 10 mg + nimesulide 100 mg, decreased wheal and flare responses significantly at 2 hrs. and this continued till 6 hrs. post-dosing. This decrease was highly significant when cetirizine was given along with nimesulide.
- **Conclusion :** The results suggest a synergistic effect exhibited by the combined use of cetirizine with nimesulide. (JAPI 1999; 47 : 389-392)

INTRODUCTION

The symptoms produced in the course of an allergic reaction, mediated by immunoglobulin E (IgE) antibodies are a result of an early specific immune response and a late reaction which appears a few minutes after the antigen challenge. This is caused by the release of soluble mediator - histamine, from the mast cells and basophils. Its release is also regulated by IgE independent mechanisms from various cell types including lymphocytes, platelets, neutrophils, monocytes and macrophages by the production of histamine release factors.[1] The late phase allergic response -is mainly due to recruitment of inflammatory cells and release of both preformed and newly formed mediators. This phase produces an amplification and prolongation of allergic symptoms induced by the initial immune response to a specific antigen.[1]

H1-histamine antagonists are used in the management of allergic conditions like urticaria, rhinitis and bronchial asthma. Most of the first generation antihistamines show good clinical efficacy in alleviating allergic symptoms, however, their use is limited by poor tolerability, predominantly due to their anticholinergic activity and sedative properties. The second generation H1i-blockers viz. cetirizine, displays a series of advantages over previous antihistamines, it is free of both sedative and cholinergic effects and has potent antiallergic activity.[2] Since the late phase of allergic response involves accumulation of inflammatory cells, use of anti-inflammatory drugs represent an important therapeutic approach in such patients. However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is not recommended mainly due to lack of protective effect against a variety of stimuli including histamine and leukotriene D4.[3] These drugs inhibit prostaglandin synthetase and may consequently increase leukotriene production,[4] which are proposed to cause bronchoconstriction. These drawbacks not only preclude the use of NSAIDs as anti-allergy drugs, but also make them unsafe for the patients of asthma.

The non-steroidal anti-inflammatory analgesic nimesulide (4-nitro-2-phenoxymethane sulfonanilide) is currently being used in the treatment of various inflammatory conditions, pain and fever states.[5] Recent animal studies indicate that nimesulide displays both antianaphylactic and antihistaminic activities providing an evidence of unusual pharmacological profile for an NSAID. The anti-inflammatory effect of nimesulide occurs through mechanisms other than prostaglandin synthetase inhibition viz. as a scavenger of oxygen free radical liberated during conversion of prostaglandin G2 to prostaglandin H2[7] and as an inhibitor of superoxide anion generation by stimulated neutrophils.[8] Nimesulide has been shown to reduce immunological release of histamine from sensitized and perfused guinea pig lungs.[9] The antihistaminic effect of nimesulide has been demonstrated using isolated guinea pig trachea preparation and by assessing the effect of nimesulide on multiphasic histamine induced inotropic responses of electrically stimulated guinea pig atria.[9]

The animal data indicates that nimesulide, in addition to antiinflammatory effect also has antihistaminic activity. Hence, the present study was conducted to evaluate if nimesulide modified the action of cetirizine on histamine induced wheal and flare response in healthy volunteers.

MATERIAL AND METHODS

Subjects

Ten healthy male volunteers were enrolled for the study after obtaining written informed consent. Their age, height and weight (mean ± SD) were 23 ± 1 years, 175 ± 2 cms and 72 ± 2 kgs, respectively. None of them had a medical history of allergy and were found to be healthy after medical examination and standard laboratory tests. The study was approved by ethics committee of the institution. Subjects were prohibited from taking any medicines or alcoholic beverages seven days before drug administration till the end of the study.

Study design and treatments

It was a randomized double blind, cross over study. Randomization was done using random number table. Cetirizine, nimesulide and placebo were dispensed as identical tablets and the investigator as well as the volunteers were not aware of the treatment given. Each fasting subject received either treatment A (cetirizine 10 mg + placebo) or treatment B (cetirizine 10 mg + nimesulide 100 mg) orally, between 08.00 am and 09.00 am on each study day according to Latin square design. After one-week wash out period subjects were crossed over.

Assessment criteria

Antihistamine activity: On four occasions (0, 2, 4, and 6 hrs. post-dosing) each volunteer received an intradermal injection of 2 µg histamine base diluted in 100 µl volume of saline on the volar surface of forearm with microlitre syringe. Wheal and flare were delineated 10 min after each injection. The outline was transferred on to a graph paper and area thus measured was expressed as square millimeter. Histamine injection and recording of wheal and flare response was done by the same investigator. Antihistamine activity was assessed by post-treatment changes in histamine induced wheal and flare areas. The effect of two treatments was compared.

Clinical safety

All adverse clinical phenomenon observed during the course of study were recorded.

Statistical analysis

The data was analysed using Student's t-test of correlated means. Intragroup comparison was done using Student's paired t-test, while intergroup comparison was done using Student's unpaired t-test. Values obtained at 0 hrs both for wheal and flare responses were considered as the control values for each volunteer.

RESULTS

Wheal

Treatment A (cetirizine 10 mg + placebo) significantly ($P < 0.01$ vs. control) inhibited wheal formation from 2h upto 6h after dosing (Table 1), similar results were obtained when treatment B (cetirizine 10 mg + nimesulide 100 mg) was administered. In this group wheal area inhibition at all the 3 post-dosing intervals was statistically highly significant ($P < 0.001$ vs. control) (Table 1).

Table 1: Effect of treatment A (cetirizine 10 mg + placebo) and treatment B (cetirizine 10 mg + nimesulide 100 mg) on histamine induced wheal and Hare response in healthy volunteers (n = 10)

	Wheal (mm^2)		Flare (mm^2)	
Time interval (hr)	Treatment A	Treatment B	Treatment A	Treatment B
0	164.7 ± 11.85	159.21 ± 11.46	1439.8 ± 215.28	1296 ± 231.52
2	124.1 ± 4.22**	50.3 ± 7.20***	1226.1 ± 172.00*	535.6 ± 120.90***
4	122.0 ± 5.96**	28.7 ± 4.37***	995.9 ± 146.80*	180.3 ± 47.75***
6	120.5 ± 5.19**	15.5 ± 4.68***	829.4 ± 158.87**	125.6 ± 4.25***

All values are expressed as Mean ± SEM

* p < 0-05, ** p<0.01, *** p < 0.001, comparisons made with control group (0 hr)

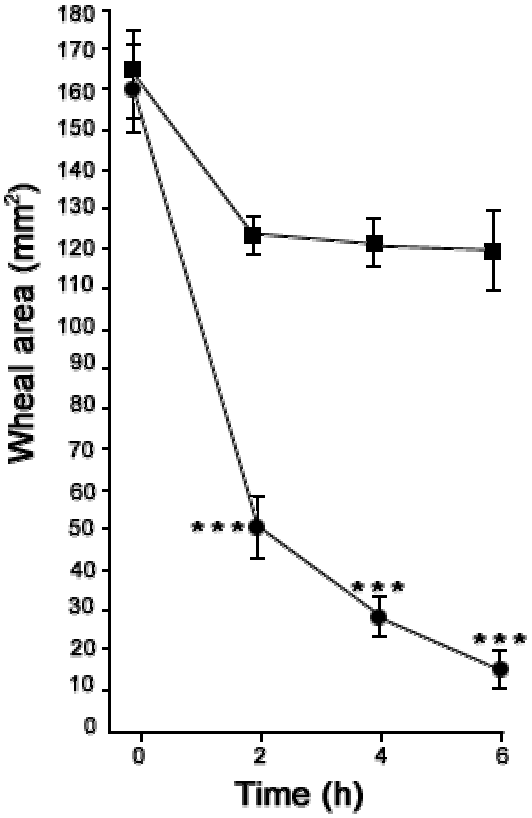

Fig. 1: Mean (± SEM) histamine - induced wheal areas (sq.mm) in ten healthy male volunteers after cetirizine 10 mg + placebo (■) and cetirizine 10 mg + nimesulide 100 mg (●). * * * p <0.001 compared to cetirizine 10 mg + placebo.

When the two treatments were compared interindividually in terms of inhibition of wheal response, it was observed that cetirizine 10 mg + nimesulide 100 mg was more effective than cetirizine 10 mg + placebo at all the 3 post-dosing intervals (P < 0.001) (Fig. 1).

It was interesting to observe that in 4 volunteers receiving treatment B (cetirizine 10 mg + nimesulide 100 mg) area of wheal was reduced to 0 sq. mm at 6 hr. post-dosing.

Flare

Cetirizine 10 mg + placebo as well as cetirizine 10 mg + nimesulide 100 mg, significantly inhibited flare formation (P < 0.05, P < 0.05, P < 0.01 vs. control) and (P < 0.001, P < 0.001, P < 0.001 vs. control) respectively 2, 4, and 6h post-dosing (Table 1).

Combination of cetirizine 10 mg and nimesulide 100 mg was more effective than cetirizine 10 mg alone (P < 0.01, P < 0.05, P < 0.05, respectively) at 2,4 and 6 hrs. post-dosing (Fig. 2) inhibiting the flare response.

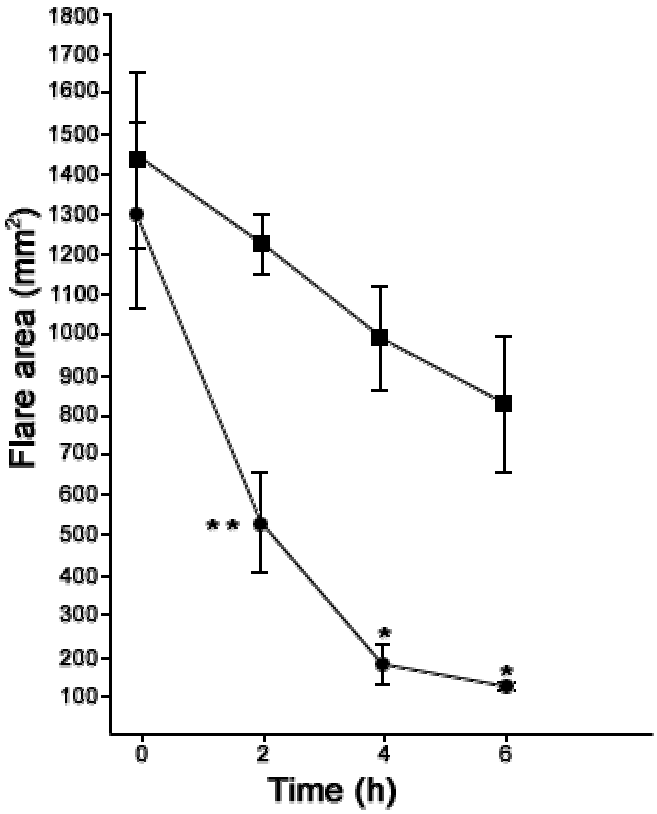

Fig. 2: Mean (± SEM) histamine - induced flare area (sq.mm) in ten healthy male volunteers after cetirizine 10 mg + placebo (■) and cetirizine 10 mg + nimesulide 100 mg (●). * p < 0.05, * * p < 0.01 compared to cetirizine 10 mg + placebo.

Safety

All volunteers enrolled in the study completed the study. All of them tolerated both the treatments well and there was no adverse event noted.

DISCUSSION

In the present study it has been observed that both cetirizine 10 mg alone and cetirizine 10 mg in combination with nimesulide 100 mg decreased wheal and flare response significantly at 2 hrs. and the response continued to decrease till 6 hrs. post-dosing. This decrease was much more when combination of cetirizine and nimesulide was given as compared to cetirizine alone. This suggests a synergistic effect exhibited by combined use of cetirizine and nimesulide.

Almost all available NSAIDs potentiate IgE mediated histamine release from basophils in vitro.[10] Indomethacin potentiated antigen induced responses in vivo[11] and in human bronchi in vitro.[12] In addition, acetyl salicylic acid, indomethacin and maclofenamic acid have been reported to reverse the inhibition of histamine release from basophils caused by adenylate cyclase agonists. The inhibition of prostaglandin synthesis through cyclooxygenase pathway of arachidonic acid metabolism is one of the recognized mechanisms of the anti-inflammatory action of NSAIDs[14] and has been proposed as pathogenetic mechanism of NSAID related adverse effects, NSAID - induced cyclooxygenase blockade may produce a shift of arachidonic acid metabolism to 5-lipooxygenase pathway with consequent increase in leukotrienes C4, D4 and E4. Moreover, 5-lipooxygenase products such as 5-hydroxyeicosatetraenoic acid, increase preformed mediators (like histamine) from human basophils[13] and 5-lipooxygenase inhibitors, inhibit IgE and non-IgE-mediated histamine release from basophils. In contrast to other NSAIDs, nimesulide and its metabo-lite 4-hydroxy nimesulide have been demonstrated to inhibit IgE and non-IgE mediated release of preformed histamine and de novo synthesis of mediators like leukotriene C4 and/or prostaglandin D2 from human basophils and mast cells. Both nimesulide as well as its metabolite have been shown to reverse the enhancing effects of acetylsalicylic acid and indomethacin on IgE mediated histamine release from basophils in vitro.[16] Another study reported that nimesulide decreased skin reactivity to histamine in healthy non-atopic individuals.[17]

This preliminary study shows the synergistic effect of the combination of nimesulide and cetirizine. There is no study reported so far showing any pharmacodynamic and pharmacokinetic interaction between nimesulide and cetirizine. Pharmacodynamic interaction seems more plausible for results obtained in the present study, as nimesulide has been reported to have both anti-inflammatory and anti-histaminic activities.[6,7,8] Studies are required in patients suffering from allergic disorders to delineate if such type of synergism existed in these patients. In that case nimesulide may be a safe and effective. NSAID for use in patients suffering from allergic disorders viz. asthma, hay fever and allergic rhinitis.

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