Comparative Efficacy of Wheal-and-Flare Suppression among Various Non-Sedating Antihistamines and the Pharmacologic Insights to their Efficacy

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Background and objective : *Non-sedating antihistamines (loratadine, fexofenadine, and cetirizine) have been widely used in Thailand. This study examined the time-of-onset and compared the 95% inhibitory effect of these agents on histamine-induced cutaneous reaction so as to understand the diversity of their efficacy.*
Patients and Method : *Thirty-one atopic patients were randomized into 4 treatment groups: placebo (n = 7), loratadine (n = 8), fexofenadine (n = 8), and cetirizine (n = 8). They were pricked with histamine every 30 min for 4 hrs. The percentage change of the wheal/flare area was calculated.*
Results : *All active treatments showed wheal suppression superior to placebo after 210 min for loratadine (P = 0,04); 90 min for fexofenadine (P = 0,009); and 60 min for cetirizine (P = 0,02), while flare suppression was significantly marked after 150 min (P = 0,0008) for loratadine; 90 min for fexofenadine (P = 0,0001); nd 60 min for cetirizine (P = 0,006). All drugs except loratadine demonstrated a 95% suppression of wheal uperior to the placebo (P = 0,001 for fexofenadine; P = 0,0001 for cetirizine). Only fexofenadine exhibited a 95% suppression of flare statistically superior to placebo (P = 0,02). Discrepancies among the effects of these 3 antihistamines were also detected.*
Discussion and Conclusion : *All antihistamines tested repressed the wheal-and-flare area superbly over the placebo within 4 hours. Cetirizine exerted the fastest onset, and it also appeared to be the most efficacious inhibitor. The heterogeneity of their efficacy probably stems from their diverse physicochemical properties, which have also been discussed.*

Keywords : *Wheal-and-Flare Suppression, Non-Sedating Antihistamines*

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Various non-sedating antihistamines including, loratadine, fexofenadine, and cetirizine have been long used in Thailand. The indications are allergic conditions affecting many organs, especially the skin and nose. One widely-accepted way to evaluate the antihistaminic activity of H1-receptor antagonists is the suppression of wheal-and-flare reactions[1-4]. Although there have been numerous reports that tested the efficacy of these antihistamines, only two studies simultaneously examined these three commonly-used agents (loratadine, fexofenadine, and cetirizine)[5,6]. Their design sometimes made it difficult to determine the time-of-onset, and furthermore, to obtain insights about their efficacy. On the contrary, the present study followed the atopic patients at 30-min intervals to compare the onset of action, and 95% suppressive effect of loratadine, fexofenadine, and cetirizine on wheal-and-flare reaction induced by histamine phosphate within a 4-hour period.

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Patients and Method

Written informed consent was obtained from all subjects prior to enrollment. The protocol and consent form for the study were reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Chiang Mai University.

Patients of both sexes (male:female = 15:16) diagnosed with allergic rhinitis and aged between 15-50 years were enrolled. They were not permitted to take any medications in a limited period (i.e., 1 week for decongestant, 2 weeks for non-sedating anti-histamine, and 4 weeks for topical or systemic steroid). They were excluded if they had (1) a history of severe asthmatic attack or anaphylaxis; (2) an excessive alcohol or coffee intake; or (3) a history of antihistamine drug allergy.

Induction and measurement of wheal-flare reactions

This method has been well described[7,8]. Briefly, histamine phosphate, 1 mg/ml (Allertech, Thailand), was applied on the volar surface of the forearm (by SK). The inciting site was 2 cm apart from previous needle pricks[9]. A disposable hypodermic needle (26 gauge) was passed through the drop and inserted into the epidermal surface at a low angle with the bevel facing up. The needle tip was then gently lifted upward to elevate a small portion of the epidermis without inducing bleeding. The needle was then withdrawn and the solution gently wiped away approximately 1 minute later to avoid smearing of the test solutions. The anaphylactic reaction was always guarded by an attending physician (SW) with an emergency kit.

Ten-minute intervals were needed to see the maximal responses of histamine phosphate. The wheal and flare were traced and transferred to paper with transparent tape[8]. Wheal-and-flare areas (W-F) were measured by an in-house developed software (by Thirasak Borisuthibandit, MD). W-F areas filled with 16-bit gray color by the Proimage® were rescaled to 300 x 300 dots per inch (DPI). Next, these graphics were entered to the software where they were replaced with alphabets (1 pixel/1 alphabet). The software then counted the exact number of alphabets in the appointed area. Eventually, according to known DPI, these pixel numbers were converted to the area in square millimeters (mm^2). The percentage inhibition was calculated by the following: [whea/flare $area_{baseline}$ - wheal/flare $area_{time\ t}$] /[whea/flare $area_{baseline}$]x 100[10].

Medications

The patients were randomly to four arms of treatment: (i) Cetirizine 10 mg (Zyrtec®, U.C.B., Thailand), (ii) Loratadine 10 mg (Clarityne®, Schering-Plough/Zuellig, Thailand), (iii) Fexofenadine 60 mg (Telfast®, Aventis/Zuellig, Thailand), and (iv) placebo (corn starch, Vidhyasom, Thailand).

Statistical analysis

The parametric statistical tests were Student *t*-test and one-way analysis of variance (ANOVA) with post *hoc* Scheffe[11]. Ninety-five percent suppressive effect among the groups was calculated by Fisher's exact test. The sample size was calculated to attain the power of the test over 80%. In this study, the power of the test was 90.9 $\pm$ 0.6 % based on the pairwise analysis of wheal inhibition. The percentage of the coefficient of variation for the method of surface area measurement was 1.91 $\pm$ 0.6%. The statistical software used for this analysis was MedCalc® version 7.1 for Windows (MedCalc Software, Belgium). Statistical significance was defined for all tests at $P < 0.05$. All comparisons were based on two-sided tests.

Results

Thirty-one patients (male = 15, female = 16) underwent the study. Age and body mass index were not statistically different among groups. They were randomized into 4 types of treatment as follows: placebo (n = 7), loratadine (n = 8), fexofenadine (n = 8), and cetirizine (n = 8). There was no statistical difference among the groups upon basal wheal and flare area. The average wheal area was 9,98 $\pm$ 5,9 mm^2, 6,65 $\pm$ 3,0 mm^2, 5,13 $\pm$ 2,7 mm^2, and 5,31 $\pm$ 2,4 mm^2 for the placebo, loratadine, fexofenadine, and cetirizine group, respectively (P > 0.05). The average flare area was 72,0 $\pm$ 32,6 mm^2, 68,35 $\pm$ 25,6 mm^2, 53,86 $\pm$ 47,7 mm^2, and 55,0 $\pm$ 41,8 mm^2 for the placebo, loratadine, fexofenadine, and cetirizine group, respectively (P > 0.05).

Onset of suppression of wheal-and-flare area by various antihistamines

Loratadine, fexofenadine, and cetirizine suppressed the wheal induced by 1 mg/ml histamine over the placebo after 210 min (P = 0,04); 90 min (P = 0,009); and 60 min (P = 0,02), respectively. Loratadine, fexofenadine, and cetirizine could inhibit the flare area over placebo after 150 min (P = 0,0008); 90 min (P = 0,0001); 60 min (P = 0,006), respectively. The percentage suppression of the individual agents is shown in Fig. 1A. At 210 min, the wheal area was reduced from the baseline to 2,81 $\pm$ 1,9 mm^2 in the loratadine group. At 90 min, fexofenadine exhibited an inhibitory effect on the wheal area from the baseline to 2,31 $\pm$ 0,9 mm^2. At 60 min, the wheal area was decreased to 3,07 $\pm$ 1,7 mm^2 in the cetirizine-treated group, while the flare size was reduced to 25,86 $\pm$ 28,9 mm^2 (at 150 min), 12,09 $\pm$ 14,4 mm^2 (at 90 min), and 16,69 $\pm$ 13,5 mm^2 (at 60 min) in

loratadine, fexofenadine, and cetirizine group, respectively. Percentage flare reduction is shown in Fig. 1B.

Among active treatments, cetirizine suppressed the wheal reaction better than loratadine at 90, 150,180, 210, and 240 min. Fexofenadine was more effective than loratadine on wheal suppression at 180, 210, and 240 min. Only cetirizine showed a superior inhibitory effect on flare size to loratadine at 90, 120, and 180 min.

Ninety-five percent suppression of wheal and flare area

With reference to the depth of inhibitory effect, 95% suppression of wheal area was found in 0 (0%), 1 (12,5%), 7 (87,5%), and 8 (100%) cases in the placebo, loratadine, fexofenadine, and cetirizine group, respectively. Whereas 95% flare suppression was observed in 0 (0%), 4 (50%), 5 (62,5%), and 4 (50%) cases in the placebo, loratadine, fexofenadine, and cetirizine group, respectively. All drugs, except loratadine, demonstrated 95% suppression of wheal superior to the placebo (P = 0,001 for fexofenadine, P = 0,0001 for cetirizine). In contrast, only fexofenadine displayed a nearly-complete suppression of flare, which was statistically superior to the placebo (P = 0,07 for loratadine, P = 0,02 for fexofenadine, P = 0,07 for cetirizine). Also, cetirizine and fexofenadine showed a significant proportion of patients with >95% suppression of wheal (but not flare) over loratadine (P = 0.001 for cetirizine, P = 0.01 for fexofenadine).

Discussion

The onset-of-action as well as depth of suppression of these 3 antihistamines reported in the present were found to be consistent with other studies[1,5,10,12,13]. Cetirizine usually showed the fastest onset (1 hr)[4]. Other active treatments were significantly more effective than placebo at 2 (for 120-mg of fexofenadine) or 3 (for 10-mg of loratadine and 60-mg twice daily of fexofenadine) hours after administration[13]. Ten-mg of loratadine sometimes demonstrated the onset of action as late as 4 or 6 hours after administration[4-5]. The present the onset as follows: cetirizine (60 min), fexofenadine (90 min), and loratadine (210 min for wheal and 150 min for flare).

In addition, cetirizine was superior to loratadine after 90 min. Simons et al[4] revealed a similar finding after 60 min. It was found that 120-mg of fexofenadine was more effective than loratadine between 2 and 6 hrs[13]. The authors found 60-mg fexofenadine demonstrated that superiority after 3 hrs. Moreover, the authors did not observe a discrepancy between fexofenadine and loratadine on flare responses. Balcer et al[14] showed that single-dose of fexofenadine (60 mg) did not suppress flares more effectively than loratadine (10 mg) until after 5 hrs. Furthermore, the difference among antihistamines was not supported by one study, in which various tested drugs (same panel as in the present study) did not differ from one another under intradermal skin testing and 2-timepoint evaluations (4 and 8 hrs)[6].

The depth of wheal suppression over 95% was found in 13 (92.8%), 5 (35.7%), and 2 (14.2%) cases taking cetirizine, fexofenadine, and loratadine, respectively. Whereas 95% of flare suppression was found in 12 (85.7%), 7 (50%), and 2 (14.2%) cases receiving cetirizine, fexofenadine, and loratadine, respectively[5].

Although the anti-allergic and anti-inflammatory effect inherent in cetirizine was believed to be

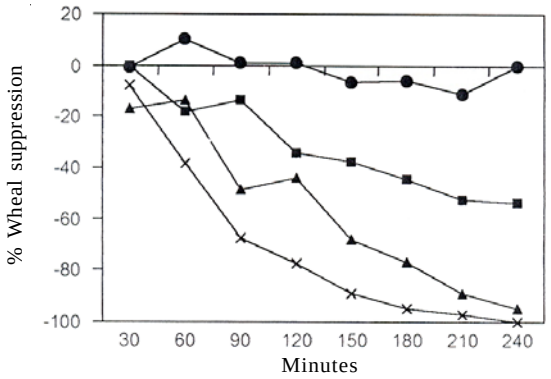

Fig. 1A Percent suppression of the wheal reaction by various treatments (circle:placebo,square: loratadine, triangle: fexofenadine, cross: cetirizine)
See the statistical significance in the text

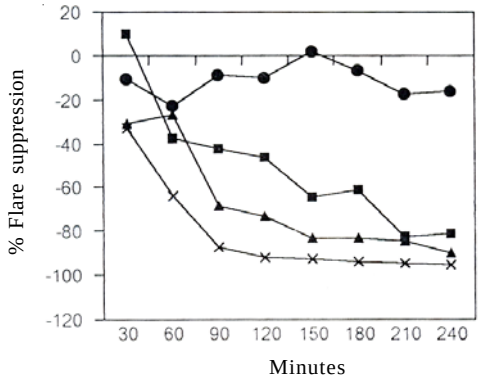

Fig. 1B Percent suppression of the reaction by various treatments (circle: placebo, square: loratadine, triangle: fexofenadine, cross: cetirizine)
See the statistical significance in the text

responsible for the superiority of cetirizine[10], the authors doubted whether or not the anti-allergic effect (i.e. mast cell stabilizing effect) of cetirizine might play a role in the model of skin reactions induced by histamine. Since histamine, which is unlike mast cell depleters (e.g. codeine or compound 48/80), does not usually produce mast cell degranulation. Therefore, the anti-allergic effect of cetirizine could not be claimed by this sort of model. The superior anti-inflammatory effect of cetirizine, which is exploited in explaining the greater effect of cetirizine is supposed to be questioned. The inflammatory responses (i.e. cell migrating events), if any, is generally delayed for hours after inciting. The anti-inflammatory action could not be declared in the very early phase, especially in the initial 60 minutes, as in the present result. Therefore, the distinctive effect of cetirizine is likely explainable from the pharmacokinetic and pharmacodynamic viewpoints. In a nutshell, the authors believe that cetirizine has a more rapid rate and greater extent of bioavailability. Also, cetirizine is of a readily active form that owns higher potency in relation to other agents.

From Table 1[8,15-20], it appears that the rate of bioavailability (as reflected by Tmax and Cmax) of cetirizine is less than that of other antihistamines. The extent of bioavailability (as reflected by AUC) of cetirizine looks prominent. Hence, it is a rationale that the manufacturer has later tended to introduce higher doses of fexofenadine. For instance, a study showed that 120- and 180-mg of fexofenadine suppressed wheal/flare area equal to 10-mg cetirizine, although a shorter duration of action was noticed by such administration[21]. It is notable that P-glycoprotein and organic anion transporter influence the bioavailability of fexofenadine[22, 23].

Besides, the presence of their active form in the tissue is covertly crucial. Cetirizine and fexofenadine have shown that their effect correlates well with high tissue:plasma concentration ratios[8,19,24], while the presence of active metabolites (i.e. desloratadine) in tissue is probably important for loratadine prior to achieving an effect[25]. Regarding drug potency, it was found that the tissue level after taking 120-mg of fexofenadine for 6 days was 5 times higher than that of 10-mg of cetirizine for 6 days[19,24]. As mentioned above, fexofenadine at this dose was not superior to cetirizine[21]. Geha[26] also revealed that the potency of cetirizine was relatively higher than that of other agents.

Table 1. Certain pharmacokinetic profiles of ntihistamines after single dose administration (8; 15-20)

Drugs	Cmax (ug/L)	Tmax (h)	AUC_{∞} (hr-ug/L)
Loratadine (10mg)	4.7	1.5	14.0
Fexofenadine (60mg)	197-210	1.7-2.1	N/A*
Cetirizine (10 mg)	257	0.5-1	2,870.0

* Not available. AUC_{∞} of 80-mg fexofenadine was 2,400 hr-ug/L

Conclusion

All tested antihistamines significantly repressed the wheal/flare area more than placebo within 4 hours. Cetirizine exerted the fastest onset. Cetirizine also appeared to be the most efficacious inhibitory agent. The heterogeneity of efficacy among these drugs probably stems from their diverse pharmacokinetic profile, active metabolite in the tissue, and the potency matter.

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การศึกษาเปรียบเทียบประสิทธิภาพในการยับยั้งปฏิกิริยาที่ผิวหนังของยาต้านฮีสตามีนชนิดไม่ก่อการง่วงนอนและความหยั่งรู้ทางเภสัชวิทยาเกี่ยวกับประสิทธิภาพของยา

สุกิจ รุ่งอภินันท์, สมพงษ์ วาจาจำเริญ, สุปราณี ฟูอนันต์

บทนำและวัตถุประสงค์ *: เนื่องจากได้มีการใช้ยาต้านฮีสตามีนชนิดไม่ก่อการง่วงนอน ได้แก่ ลอราธาดีน, ฟีโซเฟนนาดีน, เซทธัยรีซีน อย่างกว้างขวางในประเทศไทย การศึกษานี้จึงมุ่งจะตรวจสอบระยะเวลาเริ่มต้นและเปรียบเทียบความสามารถของยาที่ยับยั้งปฏิกิริยาได้มากกว่าร้อยละ 95 ต่อปฏิกิริยาผิวหนังที่เหนี่ยวนำด้วยฮีสตามีนในยากลุ่มดังกล่าว เพื่อที่จะเข้าใจความแตกต่างของประสิทธิภาพของยา*

ผู้ป่วยและวิธีวิจัย *: ผู้ป่วย 31 รายได้รับการสุ่มให้รับการรักษา 4 แบบดังนี้ ยาหลอก 7 ราย, ลอราธาดีน 8 ราย, ฟีโซเฟนนาดีน 8 ราย, เซทธัยรีซีน 8 ราย และได้รับการกระตุ้นผิวหนังด้วยฮีสตามีนทุก 30 นาทีเป็นเวลา 4 ชั่วโมง พื้นที่ส่วนนูนและรอยแดงในแต่ละจุดเวลาได้รับการคำนวณหาพื้นที่*

ผลการวิจัย *: ยาที่มีฤทธิ์ต้านฮีสตามีนทุกตัวให้ผลการยับยั้งรอยนูนเหนือกว่ายาหลอกตั้งแต่นาทีที่ 210 สำหรับลอราธาดีน (P=0,04), ตั้งแต่นาทีที่ 90 สำหรับฟีโซเฟนนาดีน (P=0,009), ตั้งแต่นาทีที่ 60 สำหรับเซทธัยรีซีน (P=0,02). ขณะที่รอยแดงได้รับการยับยั้งอย่างมีนัยสำคัญตั้งแต่นาทีที่ 150 สำหรับลอราธาดีน (P=0,0008), ตั้งแต่นาทีที่ 90 สำหรับฟีโซเฟนนาดีน (P=0,0001), ตั้งแต่นาทีที่ 60 สำหรับเซทธัยรีซีน (P=0,006) ยาทุกตัวยกเว้นลอราธาดีนแสดงการยับยั้งปฏิกิริยารอยนูนได้มากกว่าร้อยละ 95 เหนือต่อยาหลอก (P=0,001 สำหรับฟีโซเฟนนาดีน; P=0,0001 สำหรับเซทธัยรีซีน) แต่ฟีโซเฟนนาดีนเท่านั้นที่แสดงการยับยั้งปฏิกิริยารอยแดงได้มากกว่าร้อยละ 95 เหนือต่อยาหลอก (P=0,02) นอกจากนี้ยังพบความแตกต่างระหว่างกลุ่มของยาต้านฮีสตามีนด้วย*

วิจารณ์และสรุป *: ยาต้านฮีสตามีนทุกตัวยับยั้งรอยนูนรอยแดงได้ดีกว่ายาหลอกภายใน 4 ชั่วโมง เซทธัยรีซีนออกฤทธิ์เร็วที่สุด และเซทธัยรีซีนเป็นยาที่ยับยั้งได้ดีที่สุด ประสิทธิภาพของยาที่แตกต่างกันน่าจะเกิดจากคุณลักษณะทางกายภาพและทางเคมีของยาที่แตกต่างกันตามที่ได้วิจารณ์ไว้*