ISSN: 2304-2354
Number 3, Volume 44, 2013

ZYRTEC (CETIRIZINE) EFFECT ON ERYTHEMA AND WEAL INDUCED BY EPICUTANEUS SKIN PRICK TEST WITH HISTAMINE, ON HEALTHY ALBANIAN VOLUNTEERS

Kastriot Shytaj[1], Leonard Deda[2], Zhaneta Shytaj[3], Ervin Marku[4], Ervin Mingomataj[5], Engjellushe Jonuzi[6].

Rehabilitation, Technical Medical Sciences Faculty, Medical University, Tirana, Albania.
[2]Biomedical and Experimental Subjects Department, Faculty of Medicine, Medical University, Tirana. Albania.
[3]Ambulatory Service, Surgery Hospital, UHC "Mother Theresa", Tirana, Albania.
[4]Preclinical Subjects Department, Technical Medical Sciences Faculty, Medical University, Tirana, Albania.
[5] Clinic of Allergy and Clinical Immunology, UHC "Mother Theresa", Tirana, Albania.
[6]University Military Hospital, Tirana, Allbania.

Abstract

Background

Cetirizine is widely used to prevent the symptoms of allergies, especially in the skin, eye, and nose. Meanwhile Histamine Wheal and Flare inhibition is a standard biological test widely used to test the effect duration and intensity.
The aim of our study was to test the Histamine weal and flare inhibition by Zyrtec (Cetirizine) on Albanian healthy volunteers.

Method

This was an open, single dose, clinical study.
16 healthy volunteers, 5 males, with a mean age of 21+1 years participated in this study. After they received 10 mg of Zyrtec, they were tested with a skin prick test with Histamine on the forearm on thirteen occasions. Flare and weal were drowning in a transparent paper; twenty minutes after each skin prick test and the weal and flare surface were measured with software.
The data distribution were tested Shapiro–Wilk Test. Differences were analyzed with Wilcoxon Signed Ranks Test and all tests used were two-sided with significance at 5% level.

Results

The subjects have a significant inhibition of erythema only at skin prick test conducted at 1 hour post-dose ($p<0.001$). The mean time of the maximal effect achieved was 9.4+7.8 hours. None of the volunteers achieved a totally inhibited erythema.
Subjects had a significant weal inhibition at 40 minutes after dose ($p<0.001$). The mean time of the maximal effect was 6.64+1.40. All the subjects achieved a totally inhibited weal.
Both the erythema and weal inhibition was significant even at 29 hours post dose ($p<0.001$).

Discussion

The results confirmed that this product has pharmacodynamics very similar to those observed in analogue studies in other countries. As our market is full of many brands of different drugs at least for the antihistamines we may use the histamine weal and flare inhibition to evaluate its pharmacodynamical equivalence.
Key words: *cetirizine, histamine, pharmacodynamics, antihistaminics,*

Background

Cetirizine is a second generation antiH1s known to act as inverse agonist [1], and have a pharmacological effect of about 24 hours with lesser adverse effects than first generation antiH1s ancestors [2].It is widely used to prevent the symptoms of allergies, especially in the skin, eye, and nose, substituting its first generation predecessors [2].
Histamine Wheal and Flare inhibition is a standard biological test widely used to test the antihistamine effect. It can test the effect duration and intensity at the same time.
It should be noted that this effect, at least for some

ISSN: 2304-2354
Number 3, Volume 44, 2013

antihistamine drugs, may last even when the corresponding plasma concentrations are undetectable as they may have metabolites that are pharmacologically active but also as the tissue concentrations may continue to be high enough [3]. The aim of our study was to test the Histamine weal and flare inhibition by Zyrtec (Cetirizine) on Albanian healthy volunteers.

Method

This was an open, single dose, clinical study.

Materials

Study drug:

Zyrtec 10 mg tablets produced by UCB, lot 38765 were used.

For the ESPT we used a histamine solution with a concentration of 1% v/v, and single-use metallic lancets.

Transparent paper was used to trace weal and flare responses. Then the paper was scanned and the weal and flare surface were measured with KLONK-Image Measurement, Version 11.2.437516633.

Subjects

16 healthy volunteers, 5 of them were males, after they signed an informed consent and performed a routine clinical and laboratory examination entered the study. They have a mean age of 21+1 years. None of them had a chronic or acute health condition that may impact the study results. All the laboratory tests resulted normal. Their mean weights were, 62.8+10.9 kg, and height 170+8.4 cm (Table 1). The panel of the routine laboratory tests was repeated after the protocol termination.

Number of volunteers	16
Males	5
Females	11
Age *(mean ± Standard Deviation)*	21±1 years
Weight *(mean ± Standard Deviation)*	62.8±10.9 kg
Height *(mean ± Standard Deviation)*	170±8.4 cm

Table1. Studygroupcharacteristics

Study design

All received 10 mg of Zyrtec at 08:00 a.m..along with 200 ml of water, after overnight fasting. They abstained from caffeine, fruit juices and alcohols 12 hours before the experiment and for the 24-h evaluation period afterward and the plain water drinking and eating were allowed four hours after they had received the drugs.

Skin prick test

The weal and flare response were the main outcome variables of the ESPTH challenge. The skin prick test was conducted on the forearm of each volunteer on thirteen occasions (pre-dose and 0.33, 0.66, 1, 1.5, 2, 3, 4, 8, 12, 24 and 37 h post-dosing). In each case a droplet of H solution was placed on an untested part of the forearm and then the skin was pierced with a lancet. An Epicutaneus Skin Prick Test with solution 0.9 NaCl (negative control) was conducted with the first ESPTH. Flare and weal were drown in a transparent paper, twenty minutes after each skin prick test. The measurements and ESPTH were made by the same person.

Statistical Analysis

All the erythema and wheal surfaces <7 mm^2 were consider as negative, in accordance to the recommendations of the EAACI (European Academy of Allergy and Clinical Immunology) about the Allergen and Skin Test Standardizations in 1993[4]. The data distribution were tested Shapiro–Wilk Test. As the direct inhibition data were not normally distributed even after transformation, they were analyzed with non-parametric methods. Differences were analyzed with Wilcoxon Signed Ranks Test and all tests used were two-sided with significance at 5% level. The statistical analysis was performed with the PASW Statistics 18 software.

Results

Erythema inhibition

The subjects have a significant inhibition of erythema only at skin prick test conducted at 1 hour post-dose (median inhibition 35.00%, $p<0.001$). The mean maximal inhibition achieved was 97.90+2.22 %, and the mean time of the maximal effect achieved was 9.4+7.8 hours.

	Erythema	**Weal**
Time of Measured maximal effect	8 h	6 and 8 h
Mean Measured maximal effect	95.89±1.76 %	100.0±0.0%
Area under the curve (AUC_{0-t})	2396.89±814.73 mm^2*h	222.35±94.54 mm^2*h
Area under the curve (AUC_{0-t})	2569.7±108.0 $\%^2$*h	2351.7±206.8 $\%^2$*h
Area under the curve (AUC_{0-inf})	18732.6±12320.9 $\%^2$*h	5066±2320.6 $\%^2$*h

Table nr. 2. Erythemaandwealinhibitionparameters

ISSN: 2304-2354
Number 3, Volume 44, 2013

None of the volunteers achieved a totally inhibited erythema. The mean AUC0-t was 2396.89+814.73 mm^2*h. The AUC_{0-t} of the mean relative inhibition (in percentage) of the erythema was 2569.7±108.0 $\%^2$(mm)*h (Table 2). The erythema inhibition was significant even at 29 hours post dose ($p<0.001$).

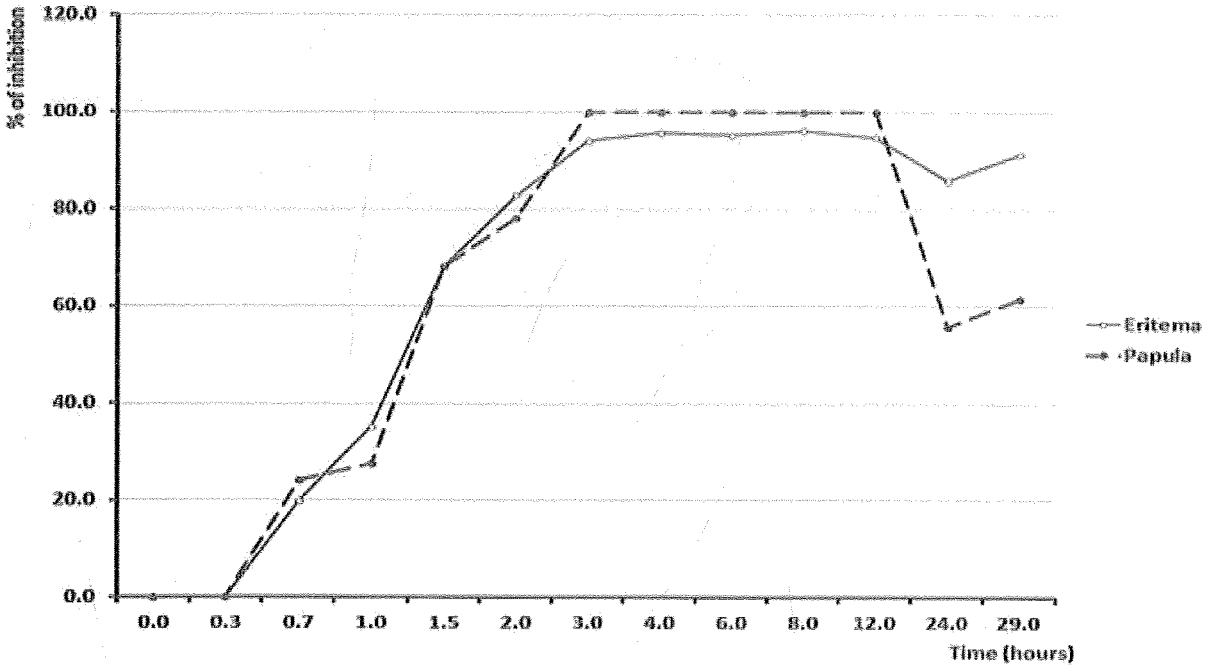

Figure nr. 1. Relative (%) median WealandFlareinhibition by Zyrtec.

Weal inhibition

Subjects had a significant weal inhibition at 40 minutes after dose (median inhibition 23.99%, $p<0.001$). The mean maximal inhibition achieved was 100% and the mean time of the maximal effect was 6.64+1.40. All the subjects achieved a totally inhibited weal. The mean AUC_{0-t} was 222.35+94.54 mm^2*h. The AUC0-t of the mean relative inhibition (in percentage) of the weal was 2351.7±206.8 $\%^2$(mm)*h (Table 2). The weal inhibition was significant even at 29 hours post dose ($p<0.001$).

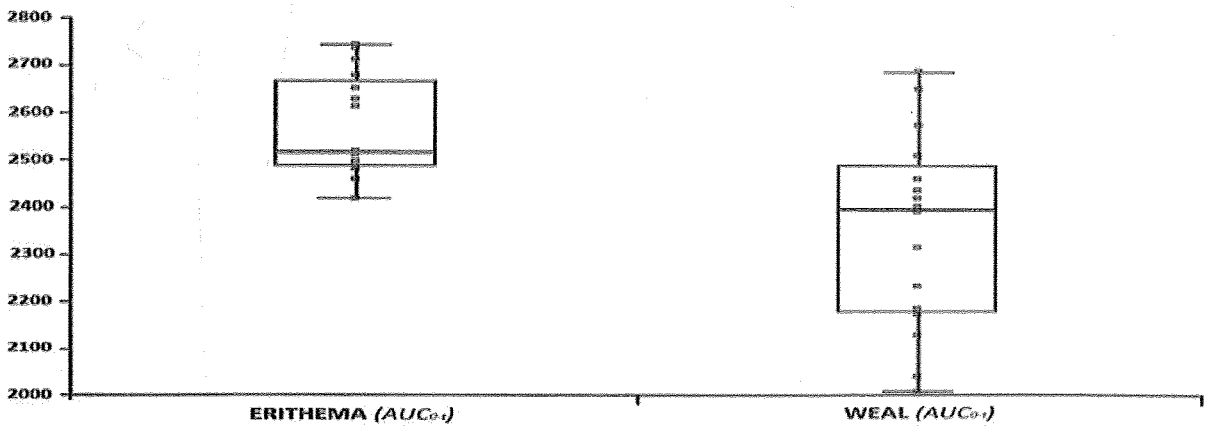

Figure nr. 2. The AUC_{0-t} of the mean relative inhibition (in percentage) ofErythemaandWeal.

Safety 3 subjects reported "moderate fatigue" after they received Zyrtec. None reported somnolence. We don't found any deviation from normal of the laboratory test after the study termination.

Discussion Histamine is the main mediator released during the acute phase of the allergic reaction. It provokes a very similar reaction, but not completely identical to that provoked by allergens in skin. These are the reasons why the skin prick test with histamine has an important role in aH studies [5],[6],[7].

The maximum effect of ESPTH can be achieved

ISSN: 2304-2354
Number 3, Volume 44, 2013

20 minutes after its application [8].The study volunteers did not suffer from any allergic disease so the ESPTH reflects the histamine effects on the skin. The study design seemed sufficiently accurate to find out the time of onset, peak and the duration of the antihistamine (Zyrtec) effect.

By the other side Cetirizine is a derivate of piperazine and at the same time a carboxylated metabolite of hydroksizine, which has three ionic forms and its distribution depends on pH[9],[10]. It is nearly completely absorbed, well-distributed in tissues except in Central Nervous System and it has a long period of elimination which enables a one dose in 24 hours prescription [11]. At the physiologic pH it exists as a "zwitterions", has a low distribution volume (0.5l/kg), a low serum concentration and a low affinity for myocardium which explains its low potential for cardiac adverse effects [12].Its dermal concentrations are relatively high, so resulting a quick and prolonged effect at this site [13], [14].

Our study shows that Zyrtec significantly inhibited the erythema only at 1 hour after dose and a weal significant inhibition at 40 minutes after dose, but the overall erythema inhibition was statistically superior to the weal inhibition, as evaluated by the comparison of the respective AUC0-t of the mean relative inhibition (in percentage). Another Cetirizine study in Albanian volunteers revealed similar results [15]. By the other side as all the subjects achieved a totally inhibition of the weal, none of them achieved a total inhibition erythema. At the same time these results are very similar to those reported by other authors [16], [17], [18], [19]. Different studies revealed a significant correlation between the histamine weal and flare inhibition and the suppression of the allergic rhinitis symptoms [20],[21].Similar to other studies, in our study the histamine weal and flare continues to be statistically significant even at 29 hours post dosing despite the fact that Cetirizine half-life is 8.3 hours[22], [23], [24].

This study evaluated the pharmacodynamics of a specific brand (Zyrtec) of Cetirizine in Albanian healthy volunteers. The results confirmed that this product has pharmacodynamics (as studied as histamine flare and weal inhibition) very similar to those observed in analogue studies in other countries. As our market is full of many brands of different drugs at least for the antihistamines we can use this simple test (histamine weal and flare inhibition) to evaluate its pharmacodynamical equivalence.

References

1. R. A. Bakker, K. Wieland, H. Timmerman and R. Leurs, "Constitutive activity of the histamine H-1 receptor reveals inverse agonism of histamine H-1 receptor antagonists," *Eur J Pharmacol,* no. 351, pp. 2203-17, 2000.
2. F. Estelle and R. Simons, "Advances in H1-antihistamines.," *N Engl J Med,* no. 351, pp. 2203-17, 2004.
3. F. Simons, H. Murray, Z. Yi and K. Simons, "Cetirizine and hydroxyzine concentrations in human skin [abstract]," *J Allergy Clin ImmunoI,* no. 93, p. 222, 1994.
4. "Allergen standardization and skin tests. Position paper. European Academy of Allergology and Clinical Immunology," *Allergy,* no. 48 Suppl 14, p. 48–82, 1993.
5. A. Purohit, C. Dacuvernelle, M. Mel, O. Benabdesselam, G. Pauli and N. Frossard, "Consistency and efficacy of cetirizine (10 mg) versus ebastine (20 mg) at 4 h on skin reactivity," *Eur J Clin Pharmacol,* no. 55, pp. 589-92, 1999.
6. A. Purohit, C. Duvernelle, M. Melac, G. Pauli and N. Frossard, "Twenty-four hours activity of cetirizine and fexofenadine in the skin," *Ann Allergy Asthma Immunol,* no. 86, pp. 387-92, 2001.
7. P. Demoly, J. Bousquet, J. Manderscheid and e. al, "Precision of skin prick and puncture tests with nine methods," *Allergy Clin Immunol,* no. 88, pp. 758-62, 1991.
8. S. Dreborg, "Histamine reactivity of the skin," *Allergy,* no. 56, p. 359–364, 2001.
9. B. Testa and A. C. P. Pagliara, "The molecular behaviour of cetirizine," *Clin Exp Allergy,* no. 27 Suppl. 2, pp. 13-8, 1997.
10. G. van Balen, G. Caron, G. Ermondi and a. col., "Lipophilicity behaviour of the zwitterionic antihistamine cetirizine in phosphatidylcholine liposomes/water systems," *Pharm Res,* no. 18, pp. 694-701, 2001.
11. F. Simons and K. Simons, "Clinical pharmacology of new histamine H1 receptor antagonists," *Clin Pharmacokinet,* no. 36, pp. 329-52, 1999.

ISSN: 2304-2354
Number 3, Volume 44, 2013

12. A. Pagliara, B. Testa, P. Carrupt and a. col., "Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H1- receptor antagonist," *J Med Chem,* no. 41, pp. 853-63, 1998.
13. L. Petersen, M. Church, J. Rihoux and a. col., "Measurement of interstitial cetirizine concentrations in human skin: correlation of drug levels with inhibition of histamine-induced skin re-pharmacosponses," *Allergy,* no. 54, pp. 607-11, 1999.
14. F. Simons, G. Sussman and K. Simons, "Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacointeraction glycoprotedynamics of the H1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria," *J Allergy Clin Immunol,* no. 95, pp. 685-93, 1995.
15. K. Shytaj, L. Deda, E. Marku, P. Bara, E. Grabocka and G. Boçari, "Differences in the histamine-induced weal and flare inhibition between cetirizine and loratadine," *PharmacologyOnline,* vol. 3, pp. 6-12, 2012.
16. P. Van Roy and M. Janssen, "Comparison of trough effects of five non-sedating antihistamines on histamine-induced weal and flare reactions," *J Allergy Clin Immunoi,* no. 87, p. 151, 1991.
17. P. Rosenzweig, H. Caplain, S. Chaufour, N. Ulliac, M. J. Cabain and J. Thebault, "Comparative weal and flare study of mizolastine vs terfenadine, cetirizine, loratadine and placebo in healthy volunteers," *Br J Clin Pharmacol,* no. 40, pp. 459-65, 1995.
18. J. J. Sienra-Monge, A. Gazca-Aguilar and B. Del RioNavarro, "Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis," *Am J Ther,* no. 6(3), pp. 149-55, 1999.
19. P. Small, "Comparison of cetirizine and loratadine in inhibiting both early and late cutaneous reactions (Abstract)," *J Allergy Clin Immunol,* no. 91, p. 244, 1993.
20. W. T. Watson, K. J. Simons, X. Y. Chen and F. E. Simons, "Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis," *J Allergy Clin Immunol,* no. 84, pp. 457-64, 1989.
21. P. H. Howarth, M. B. Emanual and S. T. Holgate, "Astemizole, a potent histamine Hi-receptor antagonist: effect in allergic rhinoconjunctivitis, on antigen and histamine induced skin wheal responses and relationship to serum levels," *Br J Clin Pharmacol,* no. 18, pp. 1-8, 1984.
22. P. Anderson, J. E. Knoben and W. G. Troutman, Handbook of clinical drug data, New York: McGraw-Hill, 2002, p. 807.
23. "www.pfizer.com," Pfizer, 2006. [Online]. Available: http:// www. pfizer. com/files/ products/ uspi_zyrtec.pdf. [Accessed 05 2013].
24. F. E. Simons, H. E. Murray and K. J. Simons, "Cetirizine and hydroxyzine concentrations in human skin," *Allergy Clin ImmunoI,* no. 93, p. 222, 1994.