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Effects of Loratadine, Cetirizine, and Terfenadine on Histamine-Induced Wheal and Erythema Responses in Normal Canine Skin

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Abstract : This crossover study was performed in order to compare the effects of cetirizine, loratadine, and terfenadine in canine skin. Five healthy dogs were used. Cetirizine 0.5 mg/kg, loratadine 5 mg and terfenadine 5 mg/kg were administered orally 4 hours before the experiment. Erythema indices and wheal size were assessed by Mexameter (MX® 18, CK, Germany) and skin reaction guide, respectively. Cetirizine-induced erythema inhibition was generally higher than other drugs and was significantly different from placebo. Cetirizine was superior to placebo at 3, 4, 5, 6, 7, and 8 minutes ($p<0.01$). Cetirizine also was superior to placebo at 9 minutes ($p<0.05$). Loratadine and terfenadine erythema inhibition were better than after placebo treatment from 4 to 9 minutes, but erythema index of terfenadine at 7 minutes was not observed probability of 95% and 99%. At 10 minutes, intradermal injection of the histamine caused a mean wheal dimension for placebo, cetirizine, loratadine, and terfenadine, which were 13.25 ± 0.75 mm, 7.5 ± 1.02 mm (53% reduction, $P<0.007$), 6.2 ± 0.58 mm (43% reduction, $p<0.01$), and 8.4 ± 0.67 mm (37% reduction, $p<0.05$), respectively, comparing with placebo. Loratadine and cetirizine were good antihistamines for clinical therapy for atopic dermatitis in dog.

Key words **:** loratadine, cetirizine, terfenadine, histamine H_1-antagonist, skin test, dog

Introduction

Atopic dermatitis has been defined as an inherited predisposition to the development of IgE antibodies to environmental allergens resulting in disease[11]. The prevalence of canine atopic dermatitis varies considerably, ranging from 3 to 30% of dermatologic case[4,17,18,20]. The treatment of canine atopic dermatitis is consisting of allergen avoidance, anti-inflammatory agents, allergen-specific immunotherapy and antimicrobial drugs. Anti-inflammatory therapy includes the glucocorticoids, antihistamines, nonsteroidal anti-inflammatory agents.

The use of conventional antihistamine drugs for treatment of canine atopic dermatitis is suggested by the hypothesis that histamine released from mast cells is a major component of the cutaneous inflammatory response[3]. Thus, antihistamines have been used in an attempt to control pruritus and skin inflammation in animals but the success has not consistent[15]. The response to antihistamine treatment varies by patient and by drugs. The H_1-antagonists are divided into first-generation antihistamines, which are chlorpheniramine, diphenhydramine, and hydroxyzine, and the second generation antihistamines include cetirizine, terfenadine, astemizole, and loratadine. The primary difference between the first- and second- generation antihistamines is that second generation antihistamines do not easily cross the blood-brain barrier. Therefore, they lack central nervous system side effects, particularly sedation, common to first-generation antihistamines. The second-generation antihistamines also do not have anti-muscarinic associated with first-generation antihistamines.

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The clinical relevance of the inhibitory effect of antihistamines is controversial[16], but an additional point of interest lies in the fact that the possible antiallergic property of these drugs confers on them a blocking action on secretion of other allergic mediators eicosanoids and cytokines[5,13]. Early studies using the histamine-induced skin reaction in human showed cetirizine, loratadine and terfenadine to be effective antihistamines[2,3,4], and numerous clinical trials have confirmed this in human[5,6,7,12]. The terfenadine showed an inhibitory action on allergen-induced wheal formation in the canine skin[1].

The objective of the study reported here was to investigate the effect of cetirizine, loratadine and terfenadine on histamine-induced wheal formation to determine their possible usefulness for treatment of atopic dermatitis in dogs and to provide a valid alternative to glucocorticoid therapy.

Materials and Methods

The five healthy adult dogs with no history of allergy were used. They were consisted of two male and three female with four white haired mixed- breed dogs and one Maltese. They were administered the anthelmintics and allowed to the commercial dog food and water freely. Their body weights were ranged between 2.6 and 5.4 kg.

Four single-dose treatments were administered: cetirizine (Cetrintab®, Daeshin Pharm Co., Korea) 0.5 mg/kg, loratadine (Loratadin®, Kukje Pharm Co., Korea) 5 mg, terfenadine (JR terfenadin®, JR Pharm Co., Korea) 5 mg/kg, and placebo capsule. Each drug was administered orally 4 hours before the start of each experiment. The doses of cetirizine and terfenadine selected were those currently approved and available at

the time of the trial. A period of approximately 7 days was chosen between each treatment to eliminate any significant carry-over effect. Dogs were refrained from eating and taking excessive exercise for 2 hours before attending the laboratory.

All dogs were sedated with 1.1 mg/kg of xylazine (Rompun®, Bayer Korea.), and 10 mg/kg of ketamine (Yuhan Keaminen®, Yuhan Co., Korea) with intravenous injection and hair of bilateral thorax was clipped with No. 10 clipper. Histamine (Sigma Chemical Co., U.S.A.), 0.05 ml of 0.01% and control vehicle (normal saline, Daehan Pharm., Korea) were injected intradermally into the surface of the lateral thorax after lateral recumbence and both side was injected by histamine and control, respectively.

Changes in skin blood flow were assessed by Mexameter (MX18, Courage and Khazaka, Germany) every minute until 10 minutes after injection of drugs. The perimeter of the wheal at 10 minutes was measured by skin reaction guide (Greer Lab, Inc., U.S.A). The experiment was performed at the same time of day in order to minimize intraindividual variation.

The significant difference between the mean values for each measurement was evaluated using Students *t*-test for paired data. A probability of 95 per cent or more was regarded as significant.

Results

Intradermal injection of histamine induced wheal and erythema responses in all dogs.

Analysis of the time course of the development of the erythema responses, repeatedly measured using Mexameter, showed the increase of the erythema index within 9 minutes after injection of histamine in placebo and all treatment groups. Erythema responses needed more time to be observed. The mean values for the erythema response to intradermal histamine challenge for all 3 treatments over 10 minutes are shown in Fig 1, 2, 3.

Cetirizine had the most rapid onset of action for inhibiting the erythema responses at 3 minutes. Inhibition of histamine induced erythema by cetirizine was generally higher than other drugs and was significantly different from placebo. Cetirizine was superior to placebo at 3, 4, 5, 6, 7, and 8 minutes ($p < 0.01$). At this time, cetirizine erythema indices were 29.25± 2.72, 48.65± 6.72, 72.30± 9.85, 77.79± 10.43, 96.38 ± 8.80, and 120.45 ± 7.59, respectively. Cetirizine also was superior to placebo at 9 minutes ($p < 0.05$) and its erythema index was 144± 5.82 (Fig 1).

Inhibition of histamine induced erythema by loratadine was apparent and pronounced from 5 to 9 minutes. Erythema indices of loratadine showed significant difference comparing that of placebo and the mean values of erythema index were 71.50± 3.73, 97.71± 3.53, 108.79± 2.88, 126.74± 2.93, and 139.17 ± 3.43, for 5, 6, 7, 8, and 9 minutes, respectively ($p < 0.01$) (Fig 2).

Terfenadine-induced inhibition of erythema indices was superior to placebo from 4 to 9 minutes. Terfenadine erythema

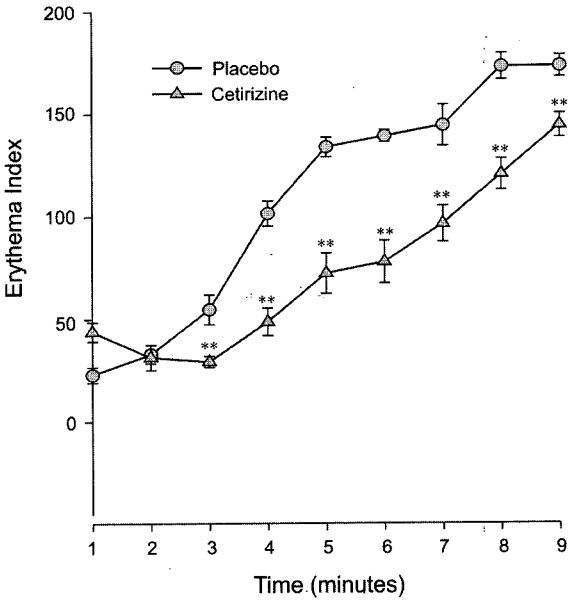

Fig 1. Effect of the treatment of placebo and cetirizine on erythema response by histamine using mexameter MX 18. Significant differences at the 95% and 99% level denoted by * and **, respectively.

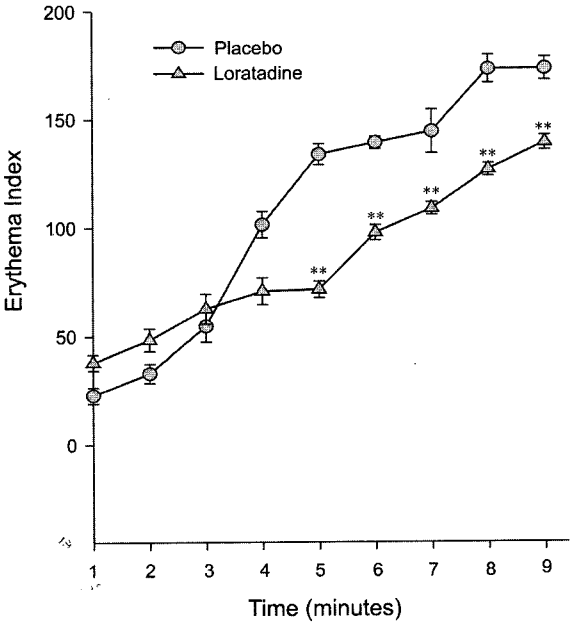

Fig 2. Effect of the treatment of placebo and loratadine on erythema response by histamine using mexameter MX 18. Significant differences at the 95% and 99% level denoted by * and **, respectively.

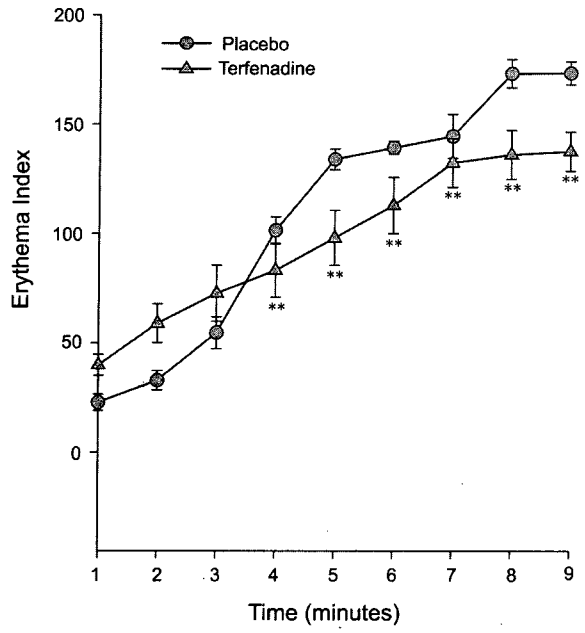

Fig 3. Effect of the treatment of placebo and terfenadine on erythema response by histamine using mexameter MX 18. Significant differences at the 95% and 99% level denoted by * and **, respectively.

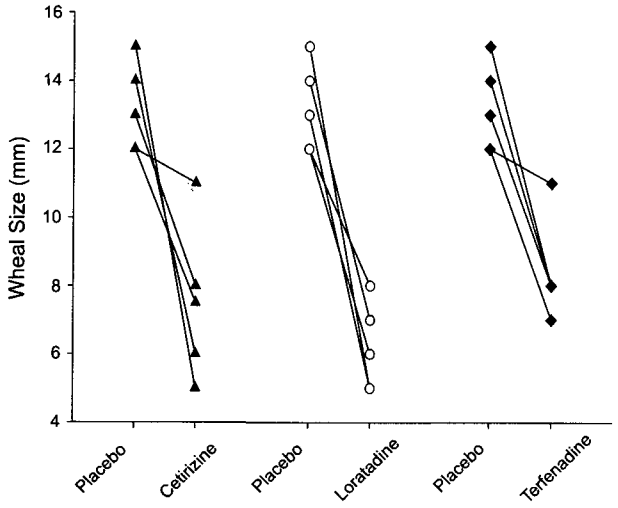

Fig 4. The conparision of individual wheal responces of each measure times after 10 minutes intradermal histamine injection. The drugs taken orally 4 h before histamine injection were placebo, certirizine, loratadine and terfenadine.

indices showed 83.15± 12.35, 98.00± 12.57, 112.84± 12.88, 135.92± 11.17, and 137.44± 8.92 for 4, 5, 6, 8, and 9 minutes ($p < 0.01$), respectively (Fig 3). However, erythema index at 7 minutes wasnt observed probability of 95% and 99%.

The surface area of wheal responses to intradermal injection of histamine for all four treatments is shown in Fig 4. At 10 minutes, intradermal injection of the histamine caused a mean wheal dimension for placebo, cetirizine, loratadine, and terfenadine, which were 13.25± 0.75 mm, 7.5± 1.02 mm, 6.2± 0.58 mm, and 8.4± 0.67 mm, respectively. The dimensions of wheal responses assessed at 10 minutes were reduced by loratadine, the mean value being 13.25 mm for the placebo group and 6.2 mm for loratadine (53% reduction, $P < 0.007$). The wheal surface dimension after administration of loratadine was smaller than for any other treatment.

Cetirizine and terfenadine had a relatively low effect but still effective with the mean wheal dimension of 7.5 mm (43% reduction, $p \leq 0.01$) and 8.4 mm (37% reduction, $p \leq 0.05$).

There were no cases of serious adverse events in this study. All treatments were well tolerated.

Discussion

Atopic dermatitis is believed to be at least partly attributable to type-1 hypersensitivity, and mast cells are among the key participants in this immune response. Histamine is a fundamental mediator released during the atopy from tissue mast cells and basophiles[3]. Histamine interacts with H_1-receptors to induce smooth-muscle contraction, enhanced capillary permeability, and neuronal stimulation with multiple secondary effects. H_1-receptor antagonists have been widely used for over 50 years in human and veterinary medicine, and these drugs have become a mainstay for management of allergic diseases. The second-generation drugs have properties of lower penetration of the blood-brain barrier with a markedly improved safety profile and infrequent adverse effects.

This study compared for the first time the most widely used drugs in dog cetirizine, terfenadine of this class as well as seldom administered drug, loratadine, with placebo in terms of erythema indices, and wheal inhibition of the cutaneous response to histamine challenge at 4 hours after drug administration. The dosage was chosen according to what was recommended and available at the time the study was conducted. This study has shown that cetirizine in dogs is a potent inhibitor of the erythema responses and loratadine is effective on the erythema responses and the wheal inhibitor resulting from the intradermal injection of histamine.

Cetirizine produced significant inhibition of erythema indices at 4 hours later. Overall, cetirizine was the most potent drug in human[2,5,7]. Cetirizine was a potent inhibition of wheal and second to loratadine in reduction. Loratadine proved a potent inhibitor of erythema indices and also produced significant inhibition of wheal responses. Terfenadine proved the least potent inhibitor of erythema indices, and wheal responses to histamine.

In vitro, Garcia et al[9] found that cetirizine which reported inhibition of anti-IgE-induced degranulation of human baso-

phils poorly inhibits histamine release from canine cutaneous mast cells. In contrast, loratadine and terfenadine proved to be more efficient at inhibiting histamine release. The ability of loratadine to inhibit histamine release is based on that loratadine and its metabolite block Ca_2^+ influx in human basophils stimulated with anti-IgE and mast cells.

However, *in vivo* experiments, we found that cetirizine significantly inhibit erythema response. Additionally, cetirizine was the second potent inhibitor of wheal. Our data for cetirizine indicate that the activity of inhibition of histamine is quite effective. Cetirizine is a good candidate for use in the treatment of atopy.

A period of approximately 7 days was chosen between each treatment to eliminate any significant carry-over effect[2] because the clinical effects persist longer than what one would expect from plasma half-life. Each half-life of cetirizine, loratadine, and terfenadine is 8-6, 8, and 3.5 hours, respectively. In people, clinical effects have persisted for 7 days after a course of treatment. In dog, 3 mg/kg of hydroxyzine inhibited skin test reactivity for 3 to 5 days after treatment was discontinued[4]. An explanation for the long duration of effect is persistence of antihistamines in tissues despite elimination from the blood. In the skin, for example, antihistamines reach high concentrations that may exceed plasma concentrations. For some drugs, the active metabolites may have a longer half-life than the parent drug.

In comparison with the consistent inhibition of histamine-induced wheal by loratadine the effects of cetirizine and terfenadine were relatively low but still effective than placebo. This result was support the Garcia et al[9] report that loratadine has potent inhibition of histamine release from dog cutaneous mast cells *in vitro*. Loratadine has the consistent inhibition of histamine-induced erythema and wheal, and also inhibition of histamine release. Loratadine, therefore, a good candidate for clinical trials.

In conclusion, a single 5 mg dose of loratadine has been shown to be an effective and consistent inhibitor of histamine-induced inflammation in the skin. In contrast, 0.5 mg/kg of cetirizine and 5 mg/kg of terfenadine afforded variable protection, being effective in some subjects, but not in orders. Therefore, based on these results second-generation antihistamines may be applied to control of pruritus of canine atopic dermatitis and provide the alternative to glucocoriticoid therapy. Further clinical trials were needed for implication of these antihistamines in canine atopic dermatitis.

Conclusions

A single 5 mg dose of loratadine has been shown to be an effective and consistent inhibitor of histamine-induced inflammation in the skin. In contrast, 0.5 mg/kg of cetirizine and 5 mg/kg of terfenadine afforded variable protection, being effective in some subjects, but not in orders. Therefore, based on these results second-generation antihistamines may be applied to control of pruritus of canine atopic dermatitis and provide the alternative to glucocoriticoid therapy. Loratadine is a good candidate for clinical trials. Further clinical trials were needed for implication of these antihistamines in canine atopic dermatitis.

References

1. Awouters F, Vermeire J, smeyers F, vermote P, VanBeek R. Niemgeers CJ. Oral antiallergic activity in *Ascaris* hypersensitive dogs: a study of known antihistamines and of the new compounds ramastine (R57959) and levocabastine (R50547). Drug Dev Res 1986; 8: 95-102.
2. Bayramgurler D, Bilen N, Apaydyn R, Et Al. Effects of acrovastine, loratadine and cetirizine of histamine-induced wheal and flare responses. Clin Exp Dermatol 1999; 24: 407-411.
3. Bachert C. Histamine-a major role in allergy? Clin Exp Allergy 1998; 28(Suppl 6): 15-19.
4. Chamberlain KW. Atopic (allergic) dermatitis. Vet Clin N Am 1974; 4: 29-39.
5. Charlesworth EN, Kagey-Sobotka A, Norman PS. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. J Allergy Clin Immunol 1989; 83: 905-912.
6. Clough G, Bennett A, Church M. Effects of H1 antagonists on the cutaneous vascular response to histamine and bradykinin: a study using scanning laser Doppler imaging. Br J Dermatol 1998; 138: 806-814
7. Devalia J, De Vos C, Hanotte F, Baltes E. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb28557 on histamine-induced cutaneous responses in healthy adult volunteers. Allergy 2001; 56: 50-57
8. De Vos C, Joseph M, Leprevost C. Inhibition of human eosinophil chemotaxis and of the IgE-dependent stimulation of human blood platelets by cetirizine. Intrn Arch Allergy Appl Immunol. 1989; 82: 212-215
9. Garcia G, Demora F, Ferrer L, Puigdemont A. Effect of H_1-antihistamines on histamine release from dispersed canine cutaneous mast cells. Am J Vet Res 1997; 58: 293-7
10. Grant JA, Danielson L, Rihoux JP, Devos C. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of histamine-induced wheal and flare response for 24h in Healty male subjects. Allergy 1999; 50: 700-707
11. Halliwell REW. Atopic dermatitis: clinical signs and diagnosis. 4th world congress of veterinary dermatology clinical program proceedings. 2000: 7-12.
12. Kreutner W, Chapman RW, Gulbenkian A. Antiallergic activity of loratadine, a non-sedating antihistamine. Allergy 1987; 412: 57-63.
13. Kreutner W, Hey J, Anthes J, Barnett A, Young S, Tozzi S. Preclinical pharmacology of desloratadine, a selective and nonsedationg histamine H1 receptor antagonist. I. Receptor selectivity, antihistaminic activity, and antiallergenic effects. Arzneimittelforschung 2000; 50: 345-352

14. Kreutner W, Hey J,Chiu P, Barnett A. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H1 receptor antagonist. II. Lack of central nervous system and cardiovascular effects. Arzneimittelforschung 2000; 50: 441-448
15. Mark GP. Antihistamines: Current Therapeutic Use. *In* Kiriks Current Veterinary Therapy XIII, 2000: 48-53.
16. Massey WA, Lichtenstein LM. The effects of antihistamines beyond H1 antagonism in allergic inflammation. J Allergy Clin Immunol 1990; 86: 1019-1024.
17. Nesbitt GH. Canine allergic inhalant dermatitis: a review of 230 cases. J Am Vet Med Assoc 1978; 172: 55-60.
18. Reedy LM, Miller WH, Willemse T. Allergic skin diseases of the dog and cat, 2nd ed. W.B. Saunders, London, UK 1997:33-44
19. Ruedisueli FL, Eastwood NJ, Gunn NK, Watson TDG. The measurement of skin pH in normal dogs of different breeds
20. Scott DW. Observations on canine atopy. J Am Anim Hosp Assoc 1981; 17: 91-100
21. Scott DW, Miller WH, Griffin CE. Small Animal Dermatology, 6th edition. W.B. Saunders Philadelphia 2001: 574-601

개 피부에서 Histamine에 의한 팽진과 발적에 대한 loratadine, cetirizine과 terfenadine의 억제효과

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요 약: 아토피성 피부염은 면역계재성 피부질환으로 소양증이 주요 증상이며 이의 치료가 필수적이다. 따라서 개에서 제2세대 항히스타민제의 임상적용을 위해 피부에 히스타민에 의해 유발된 팽진과 발적에 대한 loratadine, cetirizine과 terfenadine의 억제효과를 비교하였다. 3종의 항히스타민제는 대조군에 비해 매우 유의하게 발적반응을 억제하였으며($p<0.01$) cetirizine이 다른 제제에 비해 높은 억제효과를 보였다. 3종의 항히스타민제는 팽진 반응을 억제하는 효과를 보였으며 loratadine의 억제효과가 일정하며 지속적이었다. 따라서 제2세대 항히스타민제인 loratadine과 cetirizine은 개에서 아토피성 피부염의 소양증 치료에 적용할 수 있는 항히스타민제로 사료된다. 특히, 스테로이드제제를 대체할 수 있는 치료효과를 보일 것으로 판단된다.

주요어: loratadine, cetirizine, terfenadine, histamine H1-antagonist, wheal and erythema response, dog