Original Article

Efficacy of Levocetirizine & cetirizine in Chronic Idiopathic Urticaria in Pakistani Population.

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ABSTRACT

Objective: Comparative trial of levocetrizine and cetirizine in chronic idiopathic urticaric patients in Pakistani population.

Design: Randomized, clinical trial.

Setting: Department of Pharmacology B.M.S.I, OPD of Dermatology, JPMC, Karachi

Duration: June 2008 to December 2008.

Methods: Patients were randomized into two groups A (n=40) and B (n=40). Patients registered in each group were 15-60 years of age. Group A patients were treated with levocetirizine 5mg once daily. Group B patients were administered cetirizine 10mg. The study design was approved by ethical committee of the institution.

Results: Levocetirizine 5mg was more effective as compared to cetirizine in 90 days treatment period. The results are shown from baseline to day-90. Levocetirizine in group A reduced the itching from 2.07±0.10 to 0.17±0.06, intensity of erythema from 2.20±0.06 to 0.27±0.07, number of hives from 1.8±0.09 to 0.3±0.07, size of largest hive from 0.82±0.12 to0.17±0.06, and extent of skin involvement from1.85±.09 to 0.17±.06. Whereas Cetirizine in B group reduced itching from 2.22±0.08 to 0.42±0.07, intensity of erythema from 1.82±0.09 to 0.35±0.07, number of hives from 1.97±0.08 to 0.22±0.06, size of largest hive from 0.72±0.10 to0.20±0.06 and extent of skin involvement from 2.10±.07 to 0.32±.0.07 at day 90. There were less adverse effects of levocetirizine than cetirizine.

Conclusion: The study demonstrate that levocetrizine 5 mg was more effective as compared to cetirizine 10 mg in reducing the symptoms of chronic idiopathic urticaria; so levocetirizine was more potent as compared to cetirizine.

Key Words: Cetirizine, Levocetirizine, chronic idiopathic urticaria

INTRODUCTION

Urticaria is a common skin disorder intensely itching lesions lasting less than 24 hours or occasionally even longer. The urticaria of <6 weeks duration is arbitrarily considered, 'acute', whereas urticaria occurring >6 weeks is referred as 'chronic'[1].

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Urticaria is characterized by a well-demarcated eruption of transitory, usually itchy and sometimes even painful erythematous skin swellings that can recur for months or years. Previous investigators have defined chronic urticaria as episodes recurring for more than six weeks[2]. Urticaria and angioedema are common disorders[3]. Approximately 5% of patients with a bout of urticaria will be symptomatic for longer than four weeks. Thirty percent of patients with urticaria seen in a family practice have chronic urticaria[4]. In clinical studies percentages of causes found for urticaria vary between 20 and 90%[3,5,6].Chronic urticaria may be caused by internal diseases or malignancies, but these underlying diseases were rarely found[3,5,7,8] in the past, extensive laboratory screening has been performed to exclude

an underlying disease. Recent diagnostic guidelines recommend thorough history taking and only a very limited amount of laboratory tests[9,10].

There is no reliable prevalence data related to chronic idiopathic urticaria but it is known that 40% of cases lasting more than 6 months persist for up to 10 years and that 70% of these cases are of chronic idiopathic urticaria[11]. Cetirizine is indicated for the treatment of the uncomplicated skin manifestation of chronic idiopathic urticaria. Studies of cetirizine have demonstrated that this compound has greater selectivity for H_1 receptor and low hepatic metabolism in contrast to many other new second generation antihistamines[12].

Levocetirizine is the R-enantiomer of cetirizine, is an antihistamine with high affinity and selectivity for H_1 receptors. It reduces itching of lesions which are already present and reduce the frequency and severity of future lesions[13].

Classification of urticaria and angioedema[14].

1. Ordinary urticaria, Acute < 6 weeks' duration
2. Chronic > 6 weeks' duration, Identifiable cause (5-10%), Auto-immune (>30%), Idiopathic (50%), Physical and cholinergic urticaria, Contact urticaria (due to contact with the skin), Urticarial vasculitis, Angio-oedema[15].

The diagnosis of chronic idiopathic urticaria is based on medical history of the patient. In cases of idiopathic urticaria no etiology is recognized, symptomatic treatment should be prescribed[16].

MATERIALS AND METHODS:

A total of 80, male and female patients with sign and symptoms of chronic idiopathic urticaria were recruited from Dermatology OPD, JPMC Karachi for the study. These patients aged between 15-60 years were suffering from chronic idiopathic urticaria.Patients fulfilling the inclusion criteria were selected after informed consent.

GROUP-A (n=40) Tablet Levocetirizine at a dose of 5 mg once daily was given for 90 days.

GROUP-B (n=40) Tablet Cetirizine at a dose of 10 mg once daily was given for 90 days.

Inclusion Criteria: Patients of either sex, aged 15-60 years, the newly diagnosed cases of chronic idiopathic urticaria were included.

Exclusion Criteria: Patients with upper respiratory tract infection, physical urticaria acute sinusitis, pregnancy, lactation, complicated chronic urticaria, co-morbid conditions like diabetes heart failure, hepatic, renal impairment and patients on other medication were not included in study.

Study Procedure:

The study extended over 90 days period which was preceded by 2 weeks washout period. Subjects were assessed in washout period to determine eligibility for randomization based on pre-specified criteria. During treatment period patients were randomized to levocetirizine 5mg once daily or cetirizine 10 mg once daily for90 days with follow up visits fortnightly. The limitations of this study were that patients were randomized and it was an open trial. Patients were assessed for symptoms of chronic idiopathic urticaria fortnightly.

The Helsinki's Urticaria Rating Scale for therapeutic efficacy study medication (rated on five-point scale: Complete relief (0 score), Marked relief (1), Moderate relief (2),Slight relief (3), no relief (4), were noted at clinical visits (fortnightly). The safety and tolerability of Cetirizine and Levocetirizine were assessed by monitoring, by history and general physical examination adverse events (fatigue, headache, gastrointestinal disorders, dizziness, dry mouth) at clinic throughout the study. Statistical Analysis: All the values are taken as Mean ± SD.

The primary efficacy measurement was the mean change in the fortnightly urticaria symptom scores throughout the study period. From baseline to end point. From baseline to end point. The last observation carried forward (LOCF) approach was used and Student pair t- test was used to analyze the data.

RESULTS:

Out of total 80 patients enrolled in this study, 40 were placed in each treatment group. Demographic data is given in Table 1. Male to female ratio in levocetirizine group was 17:23 and cetirizine group was16:24. The mean ages were 33.05±1.40 years in

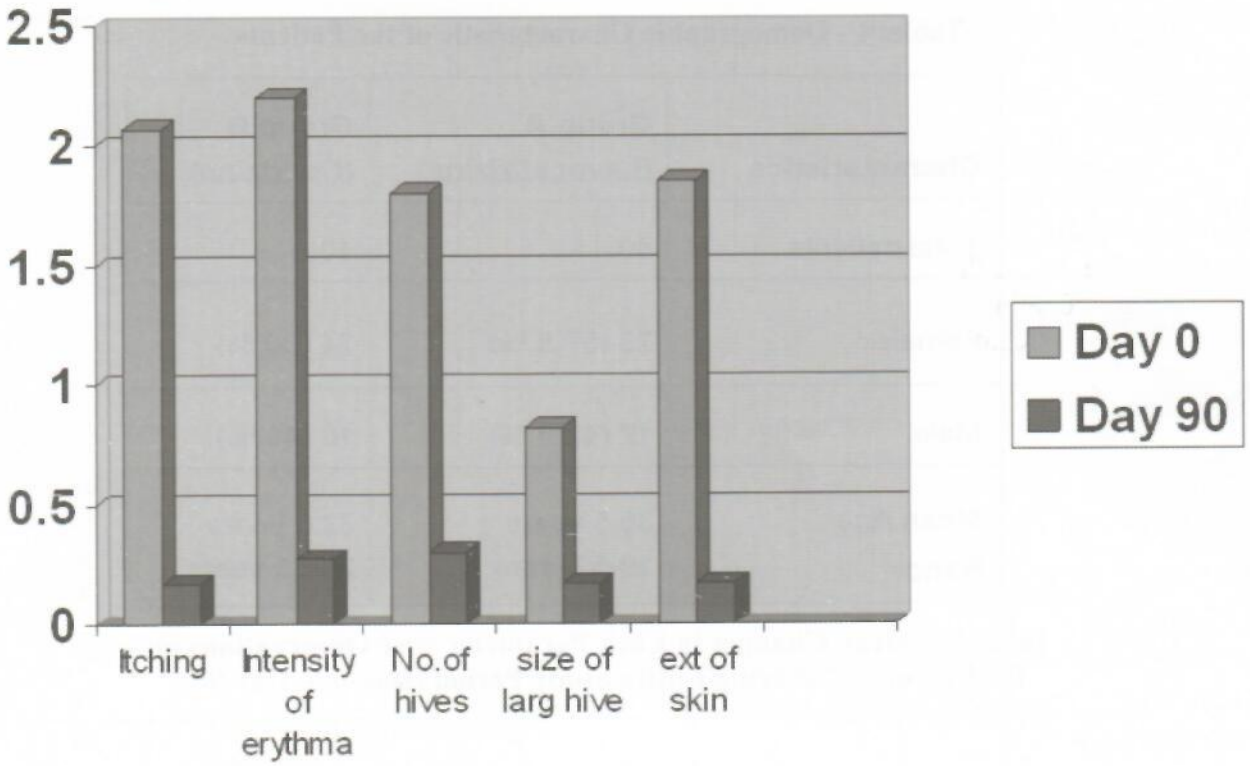
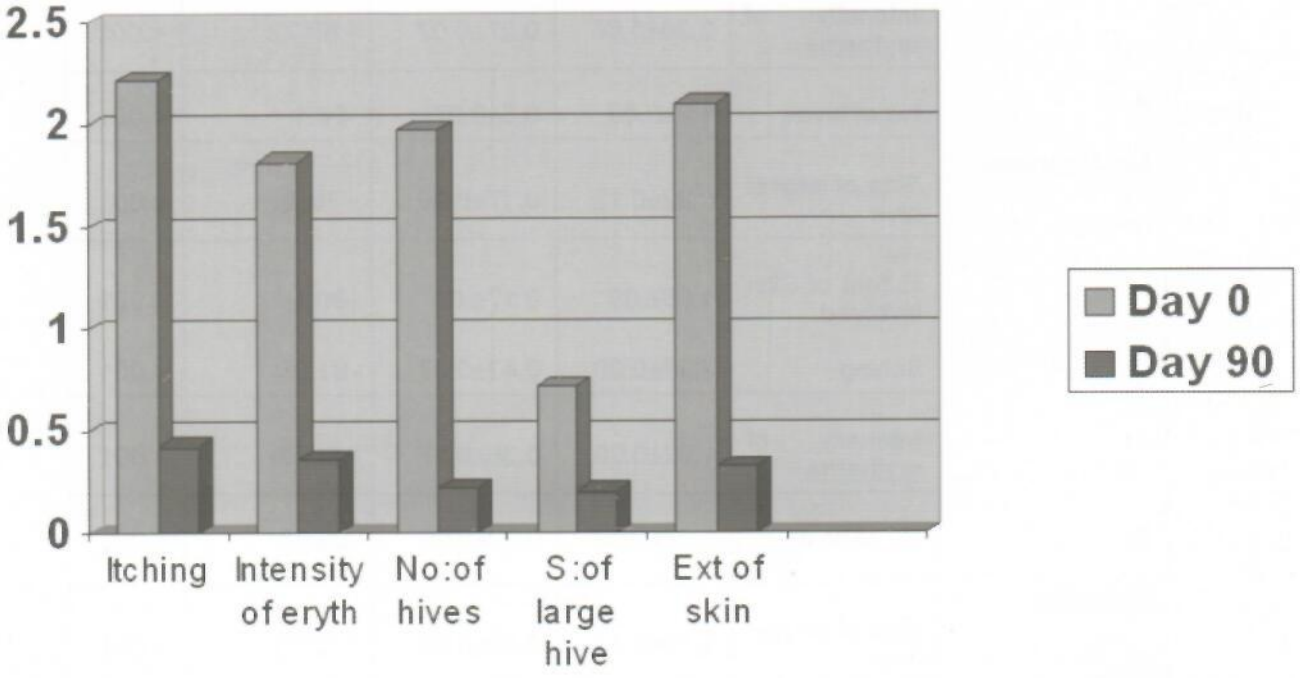


Figure- I
Changes in A Group in Each Parameter Covering Entire Study Period (Day-0, Day-45-Day-90).



Graph- II
Changes in B Group in Each Parameter Covering Entire Study Period (Day-0, Day-90).

Table: 1 - Demographic Characteristic of the Patients

Characteristics	Group A (Levocetirizine)	Group B (Cetirizine)
Total patients	40	40
Female	23 (57.5 %)	24 (60 %)
Male	17 (42.5 %)	16 (40 %)
Mean Age Range	36.5 years 19-52years	32.5 years 26-55 years

Table-II: Mean Changes in Each Parameter wise Observations in Both Groups Covering Entire Study Period (Day-0 to Day-90)

Groups	Parameter	Day-0	Day-90	Percent Change-Day0 to Day90	P-value
A Levocetirizine (n=40)	Itching	2.07±0.10	0.17±0.06	- 91.78	<.001
	Intensity of erythema	2.20±0.06	0.27±0.07	- 87.72	<.001
	No of hives	1.8±0.09	0.3±0.07	-96.1	<.001
	Size of largest hive	0.82±0.12	0.17±0.06	- 79.26	<.001
	Extent of Skin involved	1.85±.09	0.17±.06	-90.1	<.001
	Itching	2.22±0.08	0.42±0.07	-81.08	<.001
B Cetirizine (n=40)	Intensity of erythema	1.82±0.09	0.35±0.07	- 80.76	<.001
	No of hives	1.97±0.08	0.22±0.06	-88.83	<.001
	Size of largest hive	0.72±0.10	0.20±0.06	- 72.22	<.001
	Extent of Skin involved	2.10±.07	0.32±.0.07	-84.76	<.001

group A & 32.65±1.39 years in group B. Levocetirizine and cetirizine significantly reduced symptom score, (combined symptoms of itching, intensity of erythema, number of hives, size of largest hives, and extent of skin involved) after every fortnightly treatment. When end study results of both groups compared they showed significant changes effect as shown in Table –II, Graph-I &II. When data of groups compared with each other, in group A (Levocetirizine) reduced mean itching score from 2.07±0.10 on day 0 to 0.17±0.06 on day 90, the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was - 91.78%. Cetirizine 10 mg in group B reduced mean itching score from 2.22±0.08 on day 0 to 0.42±0.07 on day 90, the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was - 81.08%. In group A (Levocetirizine) reduced mean intensity of erythema score from 2.20±0.06 on day 0 to 0.27±0.07 on day 90, the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90. The average percentage reduction was - 87.72%.

Cetirizine 10mg in group B reduced mean intensity of erythema score from[1].82±0.09 on day 0 to 0.35±0.07 on day 90, the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was -80.76%. In group A (Levocetirizine) reduced mean number of hives score 1.8±0.09 on day 0 to 0.3±0.07 on day 90, the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was -96.1%. Cetirizine 10 mg in group B reduced mean number of hives score from 1.97±0.08 on day 0 to 0.22±0.06 on day 90, the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was -88.83%. In group A (Levocetirizine) reduced mean size of largest hive score from 0.82±0.12 on day 0 to0.17±0.06, on day 90 the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90. The average percentage reduction was -79.26%. Cetirizine 10 mg in group B reduced mean size of largest hive score from 0.72±0.10 on day 0 to 0.20±0.06 on day 90 the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was -72.22%. In group A (Levocetirizine) reduced mean extent of skin involvement score from 1.85±.09 on day 0 to 0.17±.06 on day 90 the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was -90.1% at day 90. Cetirizine 10 mg in group B reduced mean extent of skin involvement score from 2.10±.07 on day 0 to 0.32±.0.07at day 90 the reduction was statistically highly significant (P<0.001), when compared between day 0 and day 90.The average percentage reduction was -84.76% (p<.001), however 90 days of treatment patients in levocetirizine group and cetirizine group rated the treatment effective to patients in both groups. The most common adverse event with cetirizine was drowsiness in 4 treated patients and fatigue in 3 treated patients. The adverse effect with levocetirizine was less as compared to cetirizine.

DISCUSSION:

Chronic idiopathic urticaria is one of the most difficult skin diseases to treat being of chronic and idiopathic nature. The wheal and flare reaction in response to allergen is a very common technique routinely used by allergists to determine the sensitizing agent in allergic patients. These patients frequently take antihistamines, either on prescription or as self medication. Preventive medications are designed to reduce the frequency of itching duration or severity of urticaria attacks[17]. In current study, we conducted a comparative clinical trial of levocetirizine as well as cetirizine in chronic idiopathic urticaria patients in Pakistani population. This study shows that, levocetirizine (5mg once daily orally for 90 days) is more effective in controlling symptoms in chronic idiopathic urticaria than cetirizine given at the dosage of 10mg once daily orally for 90 days as in terms of mean reduction of total urticaria symptom score. The results appear to be reliable, both drugs were well tolerated. The results are highly statistically significant between day 0 and day 90 with a p-value (<0.001). Thus, this study indicates that levocetirizine is well tolerated and is more

effective than cetirizine. The reductions in symptom rating scores in this study coincide with the study done by Devalia JL et al[18]. A comparison with cetirizine also showed that a 2.5 mg once daily oral dose of levocetirizine inhibited the histamine-induced wheal formation almost entirely in 18 normal subjects. The inhibiting effect was comparable to that achieved with 5mg of cetirizine. The effect of levocetirizine began after approximately one hour, reached its peak six hours after administration and persisted for 28 hours. Furthermore, this study has suggested that the antihistaminic properties noted for cetirizine in the management of allergic skin conditions are likely to be due to the levocetirizine enantiomer, since this compound presents very similar pharmacodynamic profiles to those observed for cetirizine. Nevertheless, this remains to be confirmed in individuals with allergic skin conditions. The use of levocetirizine as a safe, well-tolerated, and highly efficacious drug at only half the recommended dose of cetirizine, for the treatment of allergic conditions, may be a distinct possibility in the future[18]. Our results for cetirizine are in accordance with the findings of Grant et al [19], have performed a double-blind, randomized, placebo controlled, crossover study to compare the inhibition profiles of various second-generation H1-antihistamines, including cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine, on the histamine-induced cutaneous response in 14 healthy male volunteers. All volunteers were treated with a single recommended therapeutic oral dose of each antihistamine, with a 1-week washout period between each treatment, and after treatment, they underwent the histamine skin prick test several times over a period of 0±24 h. These authors demonstrated that inhibition of the histamine-induced wheal and flare response by 10mg cetirizine was evident by 1h after treatment and was still apparent after 24h. Although 20mg epinastine was found to have a faster onset of action at 30 min after treatment, and the effects of 60mg terfenadine appeared to be comparable to those of cetirizine, analysis of area under the curve for wheal responses at 0±24 h for all drugs demonstrated that cetirizine was the most potent and loratadine the least potent of all, with a rank order of potency of cetirizine > epinastine > terfenadine > ebastine > fexofenadine > loratadine > placebo. Furthermore, they demonstrated that cetirizine caused greater than 95% inhibition of the histamine-induced wheal response in 13 of the 14 individual's investigated[19]. Simons et al[20], have compared the inhibition profiles of several antihistamines on histamine-induced wheals and flares in 20 healthy white males, and have also demonstrated cetirizine to be the most potent of all the drugs investigated, with a rank order of potency of 10mg cetirizine >120mg terfenadine > 60mg terfenadine >10mg loratadine>10mg astemizole> 4mg chlorpheniramine> placebo.

These authors demonstrated that although the inhibitory effects of cetirizine on both the wheal and flare were apparent by 30 min after treatment and lasted over the period of 24 h investigated, the effect on wheal and flare was significant by 1 and 0.7h, respectively, after treatment. However, these authors also demonstrated that cetirizine produced a maximum suppression of wheal area of 94% and flare area of 89% at 5 h after treatment[20]. An initial study on 18 healthy volunteers was conducted on a model of allergic skin reaction after histamine prick test at a concentration of 100 mg/mL. The areas, expressed in mm^2, of both the wheal and the surrounding flare were calculated at different times after the test (0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours).

Levocetirizine demonstrated higher efficacy and more prolonged action in inhibiting histamine induced wheal formation than ebastine (10 mg), fexofenadine (180 mg), mizolastine (10mg), and loratadine (10 mg)[21]. Our results are in agreement, in an initial double-blind, placebo controlled study, levocetirizine although at different dosages (2.5, 5, and 10mg)–produced a significant improvement in clinical parameters (pruritus intensity and duration, wheal number and size) in 258 patients with chronic idiopathic urticaria. The therapeutic effect of levocetirizine was significant when compared to placebo as early as the first week of treatment, and persisted throughout the entire duration of the study (4 weeks) even at the minimum dosage of 2.5 mg. 22 Subsequent studies have confirmed levocetirizine's speed of action and efficacy in 166 patients with chronic urticaria.

The objective was to measure the change induced by levocetirizine on itching severity one week and four weeks after treatment, according to a scale from 0 (no itching) to 3 (more than 6 hours of itching per day). During the first week, treatment with 5 mg levocetirizine led to a marked improvement of itching severity and a reduction in wheal number and size compared with placebo. These effects remained stable throughout the three following weeks[23]. Our observations were in agreement with a six-week double-blind, placebo-controlled study was conducted; the efficacy of levocetirizine was assessed in a population of 106 patients with chronic idiopathic urticaria at a daily dosage of 5mg. The investigation included an assessment of symptoms (pruritus; number, size and spread of the wheal lesions; number of new flare-ups, with scores of 0 to 3 according to severity) the study confirmed levocetirizine to be markedly more effective than placebo in reducing the scores of the considered scales At the end of treatment 53% of the patients who had received levocetirizine, reported total disappearance of symptoms, reduced itching intensity (85%), reduced number and spread of the wheal lesions (79% and 75% respectively) in significant percentages compared to subjects treated with placebo. Moreover, the beneficial effects of the treatment persisted up to seven days after the treatment suspension[24]. A study conducted in Germany on 17,638 subjects (24) confirmed the good tolerability of levocetirizine with a rate of 1.6% of mild or moderate adverse reactions reported during administration (fatigue, headache, gastrointestinal disorders, dizziness, dry mouth). These adverse events compromised the subjects' well being to a modest extent[25].

CONCLUSION:

The findings of this study demonstrates, levocetirizine, 5 mg once daily given by oral route , is well tolerated and more effective as cetrizine 10 mg once daily in the symptomatic treatment of chronic idiopathic urticaria patients. Overall, the benefit provided by each add-on treatment on symptom rating score was significant in both treatment groups (group A and group B).

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REFERENCES

1. Pacor M L,Lorenzo G D,Manseuto P et al. Relationship between human leukocyte antigen class I and II and chronic idiopathic urticaria associated with aspirin and/or NSAIDs hypersensitivity. Mediators of Inflammation, 2006; 6248:1-5.
2. Henz BM, Zuberbier T, Grabbe J,et al. The spectrum of urticaria. In: Urticaria: clinical, diagnostic and therapeutic aspects. Berlin: Springer Verlag; 1998.p.3.
3. Champion RH, Roberts SOB, Carpenter RH, et al. Urticaria and angio-oedema. A review of 544 patients. Br J Dermatol 1969; 81:588-597.
4. Lamberts H, Brouwer HJ, Mohrs J. Reason for encounter- and episode and process-oriented standard output from the Transition Project. Part 1and 2. Amsterdam: Amsterdam University press; 1991
5. Champion RH. Urticaria: then and now. Br J Dermatol 1988; 119:427-436.
6. Humphreys F, Hunter JAA. The characteristics of urticaria in 390 patients BrJ Dermatol 1998; 138:635-638.
7. Juhlin L. Recurrent urticaria: clinical investigations of 330 patients. Br J Dermatol 1981; 104:369-381.
8. McWhorter WP. Allergy and Risk of Cancer; a Prospective Study Using NHANESII Follow up Data. Cancer 1988; 62:451-455.
9. Friedman PS. Assessment of urticaria and angio-oedema. Clin Exp Allerqy1999; 29:109-112.

10. Bindlev-Jensen C, Finzi A, Greaves MW, et al. Chronic urticaria: diagnostic recommendations. J Eur Acad Dermatol Venereol 2000; 14: 175-180.
11. Cuvillo A D,Saster J. Use of antihistamines in peadiatics.J Invest Al Clin Imm, 2007;17:28-40. 12. Graham A. Management of chronic urticaria. Can Fam physician, 1987; 33:378-384. 13. Docrat ME.SKIN FOCUS.Current Allergy & Clinical Immunology, 2006; 19, 3.
14. Philip Clarke. Urticaria .Australian Family Physician, 2004; 33. 7; 501-503.
15. Estelle F, Simons R, Simons J K. The pharmacology and use of H1-Receptor antagonist drugs. NEJM, 1994; 330:1663-70.
16. Leznoff A. Chronic Urticaria. Can FAM Phys, 1998; 44:2170-75.
17. Frossard N, Vital-Durand D, Mounedji N, et al. Duration of the antihistaminic effect after discontinuation of ebastine. Allergy 2001; 56: 553–7.
18. Devalia JL, De Vos C, Hanotte F et al. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and UCB 28557 on histamine-induced cutaneous responses in healthy adult volunteers. Allergy. 2001; 56:50–57).
19. Grant JA, Danielson L, Rihoux Jp et al. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine, versus placebo: suppression of histamine induced wheal and ¯are response for 24 h in healthy male subjects. Allergy 1999; 54:700±707.
20. Simons FER, Mcmillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine induced wheals and fares during 24 hours in normal subjects. J Allergy Clin Immunol 1990; 86:540±547.
21. Grant JA, Riethuisen JM, Moulaert B, et al. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. Ann Allergy Asthma Immunol. 2002; 88:190–197.
22. Kapp A, Wedi B. Chronic urticaria: clinical aspects and focus on a new antihistamine, levocetirizine. J Drugs Dermatol. 2004; 3:632–639.
23. .Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patient suffering from chronic idiopathic urticaria: a randomised double blind placebo controlled parallel multicentric study. Int J Dermatol. 2006; 45:469–474.
24. Nettis E, Colanardi MC, Barra L, et al. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized double-blind placebo controlled study. Br J Dermatol.2006; 154:533–538.
25. Klimek L, Hundorf I. Levocetirizine in allergic diseases: an open multicentre practice study of efficacy and tolerability. Allergologie. 2002; 25:S1–S7.