

Cold Urticaria in Thai Children: Comparison between Cyproheptadine and ketotifen in the Treatment

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Cold urticaria syndromes are characterized by the development of urticaria and/or angioedema after cold exposure.¹ In Thai children with urticaria, 1.4% developed symptoms after cold exposure.² The diagnosis of cold urticaria is based on history of symptoms after cold exposure. Ice cube test is a simple and easy investigation to confirm diagnosis of cold urticaria.^{3,4} Cyproheptadine is one of the H₁ antagonist which is effective in the treatment of cold urticaria⁵⁻⁹ and can inhibit wheal and flare from the ice cube test after 4 weeks of treatment.³ Long term use of antihistamine may be necessary in the treatment of cold urticaria so the medication should be harmless. Cyproheptadine can depress growth in long term use in children¹⁰ so other effective drugs should be used instead of cyproheptadine. Ketotifen is an antihistamine that can prevent mast cell degranulation.^{11,12} It has been shown to prevent clinical urticaria in cold induced urticaria.^{11,13-16} Previous studies showed lack of significant side effects after prolonged use of ketotifen.^{17,18} The aims of our study were to evaluate the characteristics, laboratory findings and clinical course of Thai children with cold urticaria and

SUMMARY : The study was performed in 6 Thai children with primary acquired cold urticaria. They all suffered from generalized urticaria and two of them also had angioedema. All of them had normal erythrocyte sedimentation rate, complement 3 and negative VDRL, TPHA, hepatitis B screen and cold agglutinin titer. Cryoglobulin was checked in 3 cases and showed negative results. A double-blind cross-over study to compare the effectiveness of cyproheptadine and ketotifen demonstrated that the efficacy of cyproheptadine and ketotifen on clinical symptoms and ice cube test was not significantly different ($p>0.05$). Both of them showed good results in the treatment of cold urticaria with mild side effects. During the follow up, 5 cases showed complete recovery while the other one developed one or two exacerbations per year upon cold exposure. However, the symptoms were mild and subsided on administration of one or two doses of H₁ antihistamine. Our data demonstrated that ketotifen was as effective as cyproheptadine in the treatment of cold urticaria in Thai children.

also to compare the clinical symptoms, ice cube score and side effects between the treatment with cyproheptadine and ketotifen.

MATERIALS AND METHODS

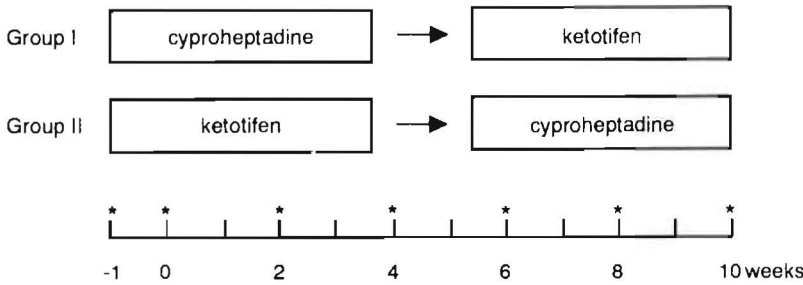
The double blind cross-over study was performed in six Thai children with primary acquired cold urticaria who were referred to the Allergy Clinic, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. On first visit, history and physical examination included ice cube test were performed. All medications were stopped for a week from first (week -1) to second

visit (week 0) as shown in the study protocol in Table 1. On the second visit (week 0) complete blood count, differential white count, stool examination, erythrocyte sedimentation rate (ESR), complement 3 (C₃), VDRL, TPHA, hepatitis B screening (HBs Ag, HBs Ab, HBcAb), cold agglutinin titer

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Table 1. The study protocol.



*= follow up and perform ice cube test.

and cryoglobulin were done. The patients were randomly divided into 2 groups (3 patients in each group). Group I: cyproheptadine (0.25 mg/kg/day divided twice daily) was started at week 0 and continued to week 4 then stopped for 2 weeks as a washed-out period. At week 6, ketotifen (Zaditen^R, Sandoz, dose < 35 kg:0.5 mg bid; ≥ 35 kg: 1 mg bid) was started and continued to week 10. Group II: ketotifen was administered first on week 0 to 4 then 2 week washed-out and 4 weeks of cyproheptadine therapy. Every visit the ice cube test was done. The clinical improvement score and side effect score were informed by the patients and their parents.

Ice cube test method

One-cubic-inch ice cube was gently placed without pressure on the ventral surface of forearm for 5 minutes. The result of ice cube test was checked at 10 minutes after the ice cube was removed and score was recorded (Table 2) by the same investigator

throughout the study. A positive ice cube test is shown in Fig. 1.

The clinical score was recorded as percent of improvement (0-100%). The clinical scores recorded were frequency of urticarial attack, size of urticarial rash, pruritus, swelling and other systemic symptoms associated with cold exposure.

The side effects such as drowsiness, dry lips, increased appetite and dizziness were scored as follows:

- 0 = no side effect
- 1 = mild side effect (no disturbance to normal activity)

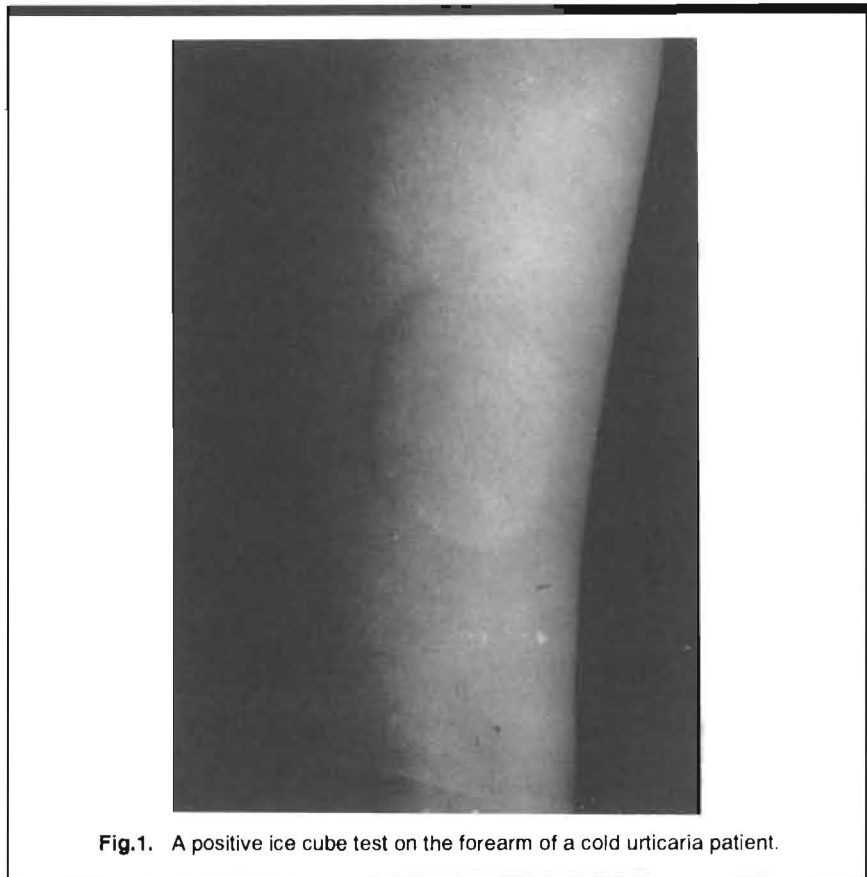


Fig.1. A positive ice cube test on the forearm of a cold urticaria patient.

Table 2. Determination of ice cube test.

Ice cube	Findings
0	none
1	red, very little edema
2	some wheal, slight raise
3	definite wheal
4	large wheal, 1/8 inch height

- 2 = moderate side effect (mild disturbance to normal activity)
- 3 = severe side effect (definite disturbance to normal activity)

The clinical and side effect scores between cyproheptadine and ketotifen were compared at 4 weeks after treatment. Ice cube scores between cypro-

heptadine and ketotifen were compared on the beginning of the treatment, at 2 and 4 weeks after treatment.

All cases were followed up for more than 5 years to study the course of cold urticaria and occurrence of other allergic disorders.

Statistical analysis

The results were analyzed by non-parametric analysis. A p value < 0.05 was considered statistically significant.

RESULTS

Characteristics of six Thai children with cold urticaria are shown in Table 3. Mean age of the patients was 7 years. Four of them were male and two were female. All of the cases suffered from urticaria for more than 6 weeks. Mean duration of urticaria before the study was 3.6 months. All of the cases had generalized urticaria while two of them also suffered from angioedema. Area of cold exposure in all of the cases was skin. Two cases also experienced cold urticaria after oral mucosa exposure to cold (ice and ice cream ingestion). None of them had history or dermographism, cholinergic urticaria, aspirin-induced urticaria or familial history of cold urticaria. Laboratory findings of the patients are shown in Table 4. Only two cases had blood eosinophil counts of more than 500 cells/mm³. Stool examination was positive for *Giardia lamblia* cysts in one case who had blood eosinophil 410 cells/mm³. He was treated with metronidazole before the study started. Cryoglobulin was done in 3 cases and all were negative.

Comparison between the results of cyproheptadine and ketotifen on clinical improvement is shown in Fig. 2. The mean percent of clinical improvement of cyproheptadine was 85 ± 6 and ketotifen was 88 ± 6 which were not significantly different (p>0.05). Comparison between ice cube scores after cyproheptadine and ketotifen treatment is shown in Fig. 3. The mean ice cube scores of cypro-

Table 3. Characteristics of six Thai children with cold urticaria.

	Patient No.					
	1	2	3	4	5	6
Age (years)	9	7	8	7	4	7
Sex*	M	F	M	M	F	M
Duration of cold urticaria (months)	3	2	3	6	2	6
Severity of symptoms**	G	G	G	G, A	G	G, A
Allergic history***	O	AR	O	Asthma	IE	Asthma
Familial allergic*** history	AR	Urt	Urt	Urt	O	AR
Area of cold exposure	skin, oral mucosa	skin	skin	skin	skin	skin, oral mucosa

* M= male, F= female
 ** G= generalized, A= angioedema
 *** AR= allergic rhinitis
 IE= Infantile eczema
 Urt= urticaria
 O= none

Table 4. Laboratory findings in cold urticaria children.

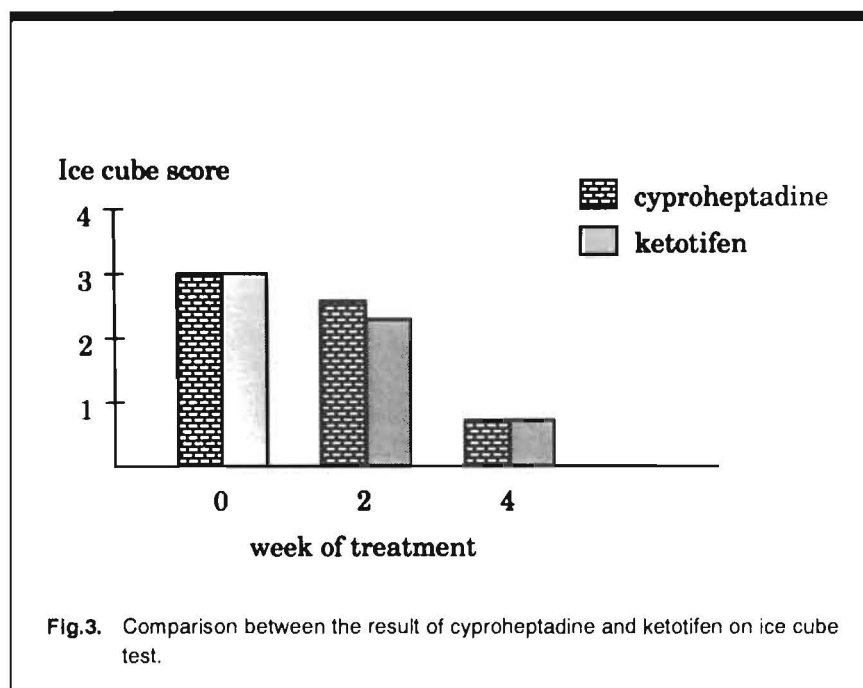
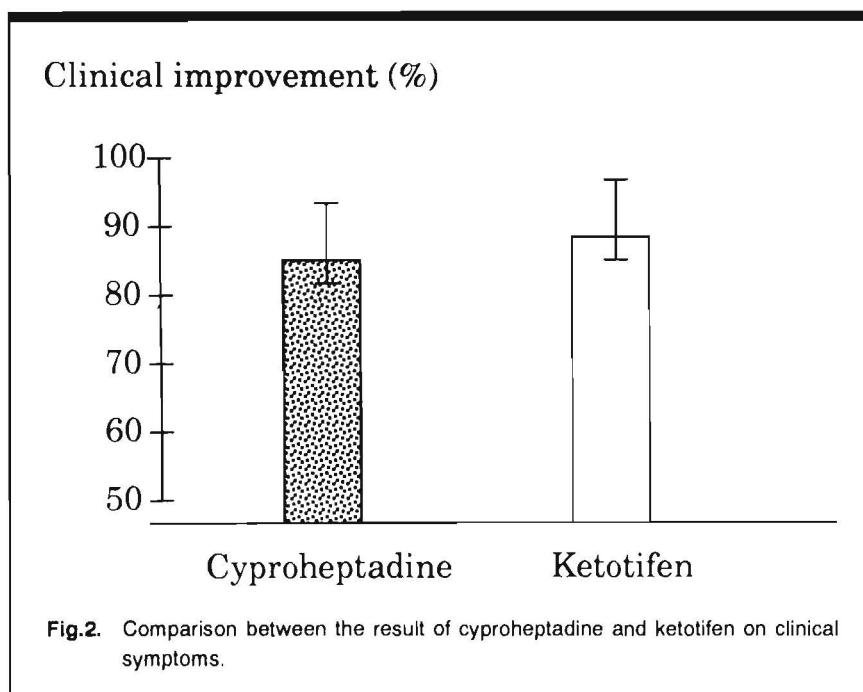
	Patient No.					
	1	2	3	4	5	6
Ice cube score	4	2	3	2	3	4
Total blood eosinophils (cells/cu mm)	410	952	0	603	0	396
Stool examination	<i>Giardia</i> cyst	N	N	N	N	N
ESR	WNL	WNL	WNL	WNL	WNL	WNL
VDRL	N	N	N	1: 1	N	N
Cold agglutinin	< 1: 64	1: 4	< 1: 4	< 1: 4	< 1: 4	< 1: 4
Hepatitis screening	N	N	N	N	N	N
C3	WNL	WNL	WNL	WNL	WNL	WNL
IgG, IgA, IgM	WNL	WNL	WNL	WNL	WNL	WNL
Cryoglobulin	N	-	N	-	-	N

N = negative
 WNL = within normal limits
 - = not done

heptadine and ketotifen before, at 2 and 4 weeks after treatment were not significantly different (p>0.05). The mean ice cube scores of cypro-

heptadine before, at 2 and 4 weeks were 3, 2.6 and 0.66 and of ketotifen were 3, 2.4 and 0.66, respectively.

Comparison between the mean side effect scores after cyproheptadine and ketotifen in Fig. 4 showed trend



that ketotifen had less frequency of side effect (4/6) compared with cyproheptadine (2/6). The mean side effect scores between these two drugs (observed along the course) after 4 weeks of treatment were 0.66 and 0.5 which were not significantly different ($p>0.05$). Only one in each drug treatment group had score as

high as 2. These side effects were drowsiness, dry lips and dizziness. One patient complained of increasing the appetite after both medications.

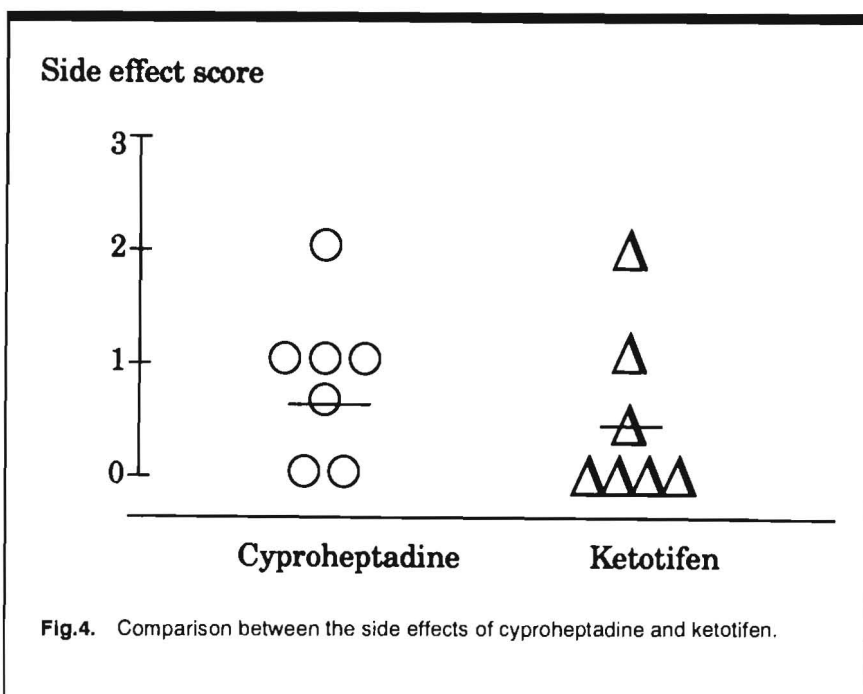
After five years of follow up, 5 cases had complete recovery. The other one showed improvement in clinical symptoms but still developed one or two episodes of cold urticaria per

year upon cold exposure. However, the symptoms was mild and subsided on administration of one or two doses of cyproheptadine or ketotifen. The clinical course of six cold urticaria children is shown in Table 5. Three of the cases have had no other allergic problems while the others suffered from asthma and allergic rhinitis.

DISCUSSION

Cold urticaria is a common form of physical urticaria. Incidence of cold urticaria is 2.5% of urticaria patients at all age groups and 74% of physical urticaria.¹⁹ Primary acquired or idiopathic cold urticaria is the most common form of cold urticaria.²⁰ Our study included six children with primary acquired cold urticaria aged 4 to 9 years old. Four of them were male. Previous studies have shown the controversy between sex distribution which may be due to the selection of the patients.²⁰⁻²² Cold urticaria may start at any age range from 1 to 74 years²⁰ but most of them develop the symptoms in young adult.

Symptoms of cold urticaria can be localized, generalized, angioedema or systemic such as tiredness, headache, dyspnea, tachycardia, collapse and even anaphylactic shock.^{20,22} In our report, four of the six patients had only generalized lesions while two of them also had angioedema. Cold urticaria usually appears after exposure to a cold, humid, windy climate or to cold water.²² Swimming in cold water may cause life-threatening cold urticaria.²² Mucosal exposure such as ice-cream ingestion may cause oral mucosal swelling and generalized urticaria or angioedema.²³ In our study, two of the patients had cold urticaria after both skin and oral mucosa exposure while the others had lesions only after skin exposure. A previous study found that 25% of cold urticaria had atopic disease²⁰ which was nearly the same as in the normal population in Finland.²⁴ Four of the patients in our study had a history of atopy and five had a

**Table 5.** Clinical course of six cold urticaria children.

	Patient No.					
	1	2	3	4	5	6
Present status*	CR	CR	CR	CR	CR	I***
Total duration of cold urticaria (months)	12	14	39	30	8	> 66
Present allergic** disorder	O	AR	O	Asthma	O	Asthma

* CR= complete recovery, I= improved
 ** O= none, AR= allergic rhinitis
 *** The patient developed one or two exacerbations of cold urticaria per year.

familial history of atopy.

The term secondary acquired cold urticaria is used if cold urticaria is associated with cryoglobulins, cryofibrinogen, cold agglutinin, paroxysmal hemoglobinuria, chronic lymphocytic leukemia, lymphosarcoma cold hemolysin or syphilis^{4, 25} while primary acquired cold urticaria is used if cold urticaria is not associated with these diseases. Almost 20% of primary acquired cold urticaria patients experience some possible triggering factors or factors that can induce symptoms just before or at the same time

that cold urticaria appears. These factors are infections such as measles, chicken pox, scarlet fever, infectious mononucleosis, ascariotic infection and respiratory viral infections.²⁵⁻³⁰ Complement fixing antibody titers to measles virus, cytomegalovirus, herpes simplex virus and *Mycoplasma pneumoniae* were significantly higher in cold urticaria patients than in controls.³⁰ VDRL, TPHA, cold agglutinin, hepatitis screening and cryoglobulin in our patients from the study were not significantly abnormal. There were no associated viral infections at the time

of inclusion and no history of such diseases just before the symptoms occurred. The previous study showed that 12% of primary acquired cold urticaria associated with dermatographism and 8% associated with cholinergic urticaria.²⁰ None of the patients from our study had history of cholinergic urticaria or dermatographism.

Symptoms of cold urticaria may develop months or years before the patients are first evaluated.²² Spontaneous recovery of primary acquired cold urticaria occurs within one and a half to two years after onset of symptoms.²² However, the symptoms may be present from a few months to 20 years or longer.^{19,22} The previous study showed that 25% of patients became asymptomatic in 1.6 years. The symptoms last more than 10 years in twenty percent of cases while in 55% of cases, the symptoms decreased and were less harmful.²⁵ The other study showed that 50% of cases were free from lesions within one year while 25% of cases had episodes more than 20 years.¹⁹ In our study the patients developed symptoms 2 to 6 months before the first evaluation. The duration of cold urticaria in our patients lasted 8 to more than 66 months. One of the cases still has urticaria once or twice a year after exposure to cold but the symptom is mild and subsides after antihistamine administration. This patient also has had moderate asthma since the time cold urticaria was diagnosed. There is currently no definitive method to predict the duration of symptoms of cold urticaria.

The definitive pathophysiology of cold urticaria is unknown. Degranulation of mast cells and release of histamine during attacks of cold urticaria have been demonstrated.³¹ Histamine has been shown to be the main mediators for immediate edema and vasodilatation in cold urticaria after cold exposure.^{8,32} It is also demonstrated that other vasoactive factors and PG D₂ would be possible candidate to have a role in cold-

induced urticaria.^{33,34}

A cardinal objective of cold urticaria management is the prevention of shock reaction during aquatic and other cold temperature exposures. Avoidance of cold exposure is important. The pharmacologic management of cold urticaria is to suppress the symptoms. H1 antihistamines are beneficial in suppressing the symptoms of cold urticaria. Cyproheptadine was the first H1 antihistamine that was shown to be effective in the treatment of cold urticaria with a double blind protocol.⁷ This study also demonstrated antiserotonin activity of cyproheptadine.⁷ Other antihistamines were demonstrated to be effective in the treatment of cold urticaria such as hydroxyzine, terfenadine, doxepin, cetirizin and ketotifen.^{8,13-16,35,36} Long term use of antihistamine may be necessary because the symptoms of cold urticaria may last many years. In children long term use of cyproheptadine can depress growth¹⁰ so the alternative drug that can be used in a long term is necessary. Ketotifen which is a mast cell stabilizer,¹⁶ antihistamine, antiserotonin,¹² acts as a calcium channel blocker and inhibits platelet activating factor,¹⁴ can reduce cold-induced histamine release.¹⁶ The effect of ketotifen in the treatment of cold urticaria was also shown in children.^{14,37} This drug can be used in long term prophylaxis of childhood asthma with low or no side effect.^{17,18} The side effects of ketotifen are stimulation of appetite, weight gain and drowsiness^{11,12} but they are much less in children than in adult. Our study demonstrated that ketotifen is as effective as cyproheptadine in treatment of cold urticaria in Thai children with lower side effects.

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