

ORIGINAL ARTICLE

Efficacy and safety of desloratadine combined with dipyridamole in the treatment of chronic urticaria

AT Khalaf, Xiaoming Liu, Wanxiang Sheng,* Jinquan Tan, AN Abdalla

Department of Dermatology, Zhongnan Hospital of Wuhan University, Wuhan, China

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*Corresponding author, Department of Dermatology, Zhongnan Hospital of Wuhan University, Wuhan 430071, China, tel. +86 15 9942 75245; fax +86 27 8733 06262; E-mail: ahmadtaha11@yahoo.com; shengwanxiang@126.com

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Abstract

Chronic urticaria (CU) imposes profound impairment on patient's quality of life. Our study was done to evaluate the clinical efficacy and safety of desloratadine combined with dipyridamole, which is a platelet adhesion inhibitor in the treatment of CU. A randomized study was done in 64 autoimmunity CU patients with positive autologous plasma skin test (APST): 34 patients as treatment and 30 controls. The treatment group was treated with desloratadine and dipyridamole, and the control group was treated with desloratadine only. The efficiency and side-effect were evaluated at the end of treatment. The levels of fragment F_{1+2} were measured by enzyme-linked immunosorbent assay in all patients at pre- and post-treatment. The clinical effectiveness rates of treatment and control group were, respectively, 85.20% (21 cured, 8 obvious effectiveness) and 70% (14 cured, 7 obvious effectiveness); they have a significant difference ($\chi = 4.09$, $P < 0.05$). Before treatment, the weals and pruritus in the treatment and control group were, respectively, $(1.74 \pm 0.90, 1.79 \pm 0.73)$ and $(1.67 \pm 0.84, 1.73 \pm 0.78)$. After treatment, the weals and pruritus in treatment and control group were, respectively, $(0.38 \pm 0.73, 0.58 \pm 0.89)$ and $(0.67 \pm 0.96, 1.10 \pm 1.12)$. These findings provide new insights into the pathogenesis of CU and suggest new therapeutic opportunities for treating this disease.

Introduction

Autoimmune chronic urticaria (CU) is emerging as a dominant cause of CU, potentially explaining up to 60% of previously idiopathic cases. CU is defined by the almost daily presence of urticaria for at least 6 weeks without an identifiable cause. Symptoms include short-lived weals, itching and erythema. CU impedes significantly a patient's quality of life. CU is an extremely distressing and disabling condition for the patient. A recent study has reported that the degree of disability experienced by a CU patient (personal, social and occupational) is similar to that of patients with severe coronary artery disease awaiting surgery.¹ There is little accurate information on the prevalence of the disease, but it is thought to affect 15% to 23% of the China population, and, internationally, the numbers are likely to be similar.^{2,3}

Pathogenic mechanisms of chronic CU have not been well understood; however, activation of skin mast cells plays a key role in inflammation associated with the disease. Mast cell activation and release of mediators, particularly histamine, can effect in cutaneous inflammatory processes and accumulation and activation of other cells. In addition, circulating cells, possibly basophils and platelets, may play a relevant role in urticaria.^{4,5} Besides their well-recognized role in haemostasis, platelets are involved in other biologic processes, including inflammation. Possible significance of platelets in urticaria may be related to their proinflammatory properties. During inflammatory and immune response, platelets may be activated and might release inflammatory mediators.

The treatment of CU represents a challenge to the physician because of the incidence of troublesome

side-effects and the recurrence of urticaria when therapy is stopped.⁶ Although antihistamines are the treatment of choice for CU, individual response to these agents is variable, can be incomplete and may be compromised by sedative and anticholinergic effects.^{7,8} More recently, minimally sedating and long-acting antihistamines have become available, and some are just as effective as older agents. Although less responsive to antihistamine therapy than acute urticaria, antihistamines are still the first line of treatment and play an important role in the management of symptomatology and at higher dosages will control symptoms in the majority of patients with urticaria.⁹ Nevertheless, second-line treatments are needed for the remaining unresponsive patients and require better investigated in double-blind, placebo-controlled trials. Several alternatives such as combinations of non-sedating H1 antihistamines with H2 antihistamines or with antileukotrienes are based on RCTs with low levels of evidence.⁹ The same holds true for monotherapy with ketotifen, montelukast, warfarin and hydroxychloroquine.

For the present study, the clinical efficacy and safety of dipyridamole, 25 mg thrice daily for 4 weeks duration, in CU has been shown in combination of desloratadine with dipyridamole in a clinical trial. Dipyridamole is a platelet adhesion inhibitor, although the mechanism of action has not been fully elucidated. The mechanism may relate to inhibition of red blood cell uptake of adenosine, itself an inhibitor of platelet reactivity, phosphodiesterase inhibition leading to increased cyclic-3,5-adenosine monophosphate within platelets, and inhibition of thromboxane A2 formation, which is a potent stimulator of platelet activation. Desloratadine is reported to be a potent, non-sedating antihistamine that is an active metabolite of the H1 antihistamine loratadine. It has been shown to relieve symptoms and signs of CU. Many *in vitro* studies have shown that desloratadine has direct effects on inflammatory mediators in human cells.^{10,11}

Materials and methods

These 64 subjects with CU the autologous plasma skin test (APST positive) randomized, double-blind; parallel group study was carried out in Zhongnan Hospital of Wuhan University, Wuhan, China. The study group (male, 27 cases; female, 37 cases; 3.25–71, age; 0.25–17 years, duration of disease) divided into 30 control and 34 treatment groups. Their disease was characterized by continuous or recurrent spontaneous weals having appeared for more than 6 weeks.

All subjects were at least 16 years old and had a documented history of CU of at least 6 weeks' duration and with a frequency of at least three episodes per week

in the absence of treatment. Each episode of urticaria was defined as weals of varying size of no more than few hours' duration. Long-term corticosteroids have been stopped 1 month before the screening visit, also any drug used for the prevention and treatment of CU 1 week before.

The following patient categories were excluded: cholinergic urticaria, drug-induced urticaria, urticarial vasculitis, physical urticaria, pregnant or lactating women, and any factor that may affect drug absorption, distribution, metabolism and excretion. At the first visit, a complete medical history was taken for each patient. A clinical examination [including electrocardiogram (ECG), blood pressure, etc] with a standard laboratory tests was also carried out at inclusion and repeated after 1, 2 and 4 weeks of treatment.

Baseline characteristics of the groups were similar: gender ($t = 0.55$, $P > 0.05$), age ($t = 0.74$, $P > 0.05$), duration of disease ($t = 0.75$, $P > 0.05$), and there was no significant difference in symptom scores ($t = 0.61$, $P > 0.05$).

Drug administration

The treatment group was treated with 5 mg/d qd desloratadine and 25 mg thrice daily dipyridamole.

The control group was treated with 5 mg/d qd desloratadine and placebo. Both of them had been treated for 28 days.

Where

- Desloratadine tablets

Brand Names: Diluleitading Pian Produced by seaside Pharmaceutical Company Ltd of Shenzhen (city in China)

- Dipyridamole tablets

Brand Names: Shuangmidamo Pian Produced by Yongda Drug Manufactory in Jiangsu province

Efficacy criteria (symptom and signs scores)

Patient's symptoms and signs recorded according to GA²LEN/EAACI guide lines as shown in Table 1.¹²

Meanwhile, patient's symptoms and signs assessment before and after 4 weeks of treatment were according to Symptom Score Reduce Index (SSRI).

$$\text{SSRI} = (\text{total score before treatment} - \text{total score after treatment}) / (\text{total score before treatment}) \quad (1)$$

The validity of clinical treatment effect according to SSRI:

Invalid SSRI < 0.20,

Effective: $0.60 > \text{SSRI} \geq 0.20$,

Obvious effective: $0.90 > \text{SSRI} \geq 0.60$,

Clinical cure: $\text{SSRI} \geq 0.90$.

The rate of affectivity is the combined clinical cure and obvious effect divided by total.

Table 1 Assessment of disease activity in urticaria patients

Score	Weals	Pruritus
0	None	None
1	Mild (< 20 weals/24 h)	Mild
2	Moderate (21–50 weals/24 h)	Moderate
3	Intense (> 50 weals/24 h or large confluent areas of weals)	Intense

Sum of score: 0–6.

Safety criteria

Blood pressure and heart rate were measured; ECGs and complete clinical check were done before treatment; in addition to patient's blood, urine ALT, urea, creatinine, etc. were inspected on the first visit. In addition, analysis done at 7, 14 and 28 days after the beginning of treatment, effectiveness and adverse effects were observed. Adverse effects were defined as clinical signs or symptoms that appeared or worsened during treatment. Abnormalities in laboratory parameters and vital signs that lead to withdrawal of treatment were also recorded.

Analysis of results

Analyses were done using Statistical Package for Social Sciences (SPSS) 11.5 software on an intention-to-treat basis. Quantitative variables were presented as means and standard deviations and categorical or dichotomous variables as absolute or relative frequency by class. Where global treatment effects were significant, two-by-two comparisons were done at a significance level of 5%.

Pruritus scores, as well as the number of weals of urticaria per day and the mean total urticarial score, were analysed using *t*-test. In addition, an analysis was also done whereby changes in mean total scores from days 0 to 7 to ascertain whether improvements were reported earlier with treatment.

Table 2 CU patients with symptoms and signs scores

Groups	Cases	Before treatment		After treatment		t_1	P_1	t_2	P_2
		Weals	Pruritus	Weals	Pruritus				
Treatment	34	1.74 ± 0.90	1.79 ± 0.73	0.38 ± 0.73	0.58 ± 0.89	16.41	< 0.001	0.34	> 0.05
Control	30	1.67 ± 0.84	1.73 ± 0.78	0.67 ± 0.96	1.10 ± 1.12	9.02	< 0.001	3.34	< 0.01

t_1, P_1 values of the same group before and after treatment; t_2, P_2 values between the two groups.

Table 3 Clinical effectiveness

Group	Cases		
	Cured	Obvious effective	Total effectiveness percentage
Treatment group	21	8	85.20
Control group	14	7	70.00

They have significant difference ($\chi = 4.09, P < 0.05$).

Statistical analysis

Descriptive statistics and comparisons between treatment and control groups (*t*-test) were done at d_0 and at the last observed value in the study d_{end} and on the difference between these two values. The parameters measured were between two groups of diameter of the largest weal, number of weals, appearance of weals, frequency, weal duration and plasma prothrombin fragment. F_{1+2} *t*-test was used to compare the results of the testing; 0.05 for the difference was significant. $P < 0.05$ has already shown the difference.

Results

Clinical effectiveness

Signs and symptoms of CU patients before and after treatment ($\bar{x} \pm s$) are shown in Table 2.

The total clinical effectiveness rates between the two groups are shown in Table 3.

Plasma prothrombine

Table 4 shows that CU patients' plasma F_{1+2} levels have obvious improvement after treatment.

Relapse after withdrawal

After stopping treatment for 1 week, the patient developed itching or weal without a definite cause; thus, it is called a relapse.

Table 4 CU patients' F_{1+2} levels

Group	No. cases	Before	After	t	P
APST + ve	64	3.27 ± 2.74	0.87 ± 0.46	9.93	< 0.001
Treatment group	34	3.34 ± 2.74	0.94 ± 0.58	6.94	< 0.001
Control group	30	3.19 ± 2.64	1.15 ± 1.12	7.03	< 0.001

In the clinical treatment group cured, recurrence rate is 23.81% (21 cases) after stop of 4-week treatment.

Fourteen cured cases of the control group healed upon withdrawal 4 weeks after (clinical recurrence rate of 52.94%).

Chi-squared test: $\chi^2 = 4.63$, $P < 0.05$; the two groups of patients with clinical symptoms were significantly different.

No serious adverse effects

The main adverse reactions in patients account for the mild drowsiness, headache, dizziness, dry mouth, gastrointestinal discomfort, but they are tolerable. Withdrawal symptoms did not affect their daily lives and work. Laboratory examination showed no abnormality in the two groups before and after treatment.

Discussion

Whereas the older, first-generation antihistamines, such as chlorpheniramine and hydroxyzine, are effective in the symptomatic relief of CU in many patients, newer agents with comparable efficacy, superior tolerability (particularly with respect to sedation and anticholinergic effects) and the convenience of once daily administration have now become widely available. The efficacy and safety of antihistamines in urticaria is undisputed, although not all patients respond, and some, very occasionally, become worse. Alternative treatment should be considered for cases of CU resistant to high-dose antihistamines. This study showed that the antihistamine desloratadine combined with dipyridamole, which is a platelet adhesion inhibitor, are more effective and superior to desloratadine alone in the management of patients with CU. Desloratadine, long-term tricyclic non-sedative antihistamine, is the active metabolite of loratadine. It is selective peripheral H1-receptor antagonist, also have anti-inflammatory action.

The second-line therapy for CU after antihistamines includes a wide range of drugs such as corticosteroids, cyclosporin, doxepin, dapsone, androgens and calcium antagonists.^{13–17} Interestingly, published studies showed that warfarin, an anticoagulant drug, induced a dramatic response in some patients with CU unresponsive to antihistamines in a double-blind, placebo-controlled study.¹⁸

Furthermore, published case reports showed the effectiveness of heparin as a treatment for CU.¹⁹ This supported the possibility that patients with CU could derive clinical benefit from dipyridamole, and therapy may interfere with pathogenic mechanisms involved in CU. Evidence supporting this was obtained in our study in which the clinical effectiveness rates after 4 weeks of treatment were higher in the treatment group (desloratadine plus dipyridamole), 85.20% (21 cured, 8 obvious effectiveness), than the control group (desloratadine alone), 70% (14 cured, 7 obvious effectiveness); they have significant difference ($\chi = 4.09$, $P < 0.05$). Furthermore, Plasma levels of F_{1+2} were measured by sandwich enzyme-linked immunosorbent assay in all patients at pre- and post-treatment. The results show that the F_{1+2} plasma levels were related to urticaria severity at the time plasma was collected. The levels of F_{1+2} in patients have been decreased obviously after treatment (3.27 ± 2.74 vs. 0.87 ± 0.46 , $P < 0.001$). This strongly suggests that CU is associated with the generation of thrombin, and that the severity of the disease is paralleled by the amount of thrombin generated. These results pointed to a possible role by platelet-derived or clotting factors in the skin reactions.

Under normal circumstances, coagulation and fibrinolytic system maintain a balance state. The prothrombin activation fragment F_{1+2} is an index of *in vivo* thrombin generation; one molecule of F_{1+2} is released with the generation of each thrombin molecule.^{20–22} Anticoagulation suppresses the F_{1+2} level in a dose-response fashion.²³ It has been shown that CU patients showed high blood coagulation state with F_{1+2} levels higher than normal.²⁴ The mechanism may be excessive activation of mast cells in patients with CU. Histamine is released with a wide variety of inflammatory mediators, including cytokines, and then activates plasma prothrombin to thrombin. Blood platelet significance in inflammation is recognized but poorly characterized in urticaria. It is known that platelets are activated during inflammatory processes and are involved in modulating inflammatory and immune response via various mediator releases. Platelets have been described as a source of inflammatory mediators that are implicated in histamine release from basophils and mast cells.²⁵ Interestingly, data from experimental study prove that PF-4 fragment is able to induce rat mast cells to histamine release in a dose-dependent manner.²⁶

Dipyridamole inhibits phosphodiesterase; this causes relative increase in the concentration of intracellular cAMP, thereby suppressing the degranulation of mast cells or basophils. An active role in the release of subsequently inhibited plasma prothrombin to thrombin into small elements corresponding to reduce F_{1+2} ,²⁰ this is in agreement with the experimental results of the study. Moreover, it has been shown that histamine is released by human

platelets in response to aggregatory and immunological stimuli. In turn, exogenous histamine potentiates platelet activity measured by the aggregation induced by different agonists, acting through histamine receptors.²⁷ Meanwhile, mutual dipyridamole can inhibit platelet aggregation and platelet membrane and adenosine diphosphate (ADP), and high concentrations inhibit collagen, thrombin and epinephrine-induced platelet release reaction. PG₁₂ also enhance the synthesis of endogenous anticoagulant effect. Therefore, in patients with prothrombotic CU, using PG₁₂ as indicators for monitoring the severity and efficacy remains to be further studied.

Finally, the results of the current study seem to open some new insights into the management of CU. To the best of our knowledge, there have been no published reports of the effectiveness of dipyridamole as a treatment for CU. The side-effects noted during the therapy were relatively minor and tolerable and did not affect patients' daily lives and work. None of the side-effects required discontinuation of the therapy. Laboratory examination showed no abnormality in the two groups before and after treatment. But observation time is short, and long-term effects of medication on plasma thrombin delay further observations.

Conclusion

The management of CU has always been a major problem for both physicians and their patients. Although antihistamines are the mainstay of pharmacologic therapy for urticaria, they are not always sufficient, especially for the chronic autoimmune type. This study showed that the antihistamine desloratadine combined with dipyridamole are more effective and superior to desloratadine alone in the treatment of CU with no severe side-effects. Moreover, elevated levels of plasma prothrombin F₁₊₂ may play an important role in the pathogenesis of CU.

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