

# High-dose levocetirizine for the treatment of refractory chronic spontaneous urticaria and the effect on the serum inositol triphosphate level

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## Abstract

**Objective:** The second messenger inositol triphosphate (IP3) is involved in signal transduction in multiple cell types. We evaluated the effects of high-dose levocetirizine on chronic spontaneous urticaria (CSU) and examined the significance of serum IP3 level in the pathogenesis of CSU.

**Methods:** Fifteen patients with refractory CSU were given oral levocetirizine at a dose of 15 mg once daily for 7 days, and treatment efficacy was determined using the Urticaria Activity Score and by evaluating wheal-and-erythema reactions and itching. The serum concentration of IP3 at specific time points was determined by enzyme-linked immunosorbent assay.

**Results:** The mean serum concentration of IP3 was  $43.54 \pm 41.97$  pg/mL prior to treatment,  $18.40 \pm 17.53$  pg/mL after treatment, and  $1.31 \pm 0.92$  pg/mL in a healthy control group. The mean concentration of IP3 was significantly higher before treatment than after treatment, and the level of IP3 in the patient group before and after treatment was significantly higher than that in the control group.

**Conclusion:** High-dose levocetirizine was shown to be effective in the treatment of CSU. The level of serum IP3 was positively correlated with CSU activity, indicating that IP3 may play an important role in the pathogenesis of this condition.

## Keywords

Chronic spontaneous urticaria, levocetirizine, inositol triphosphate, high-dose antihistamine, efficacy index, second messenger

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## Introduction

Inositol triphosphate (IP3) is a second messenger widely used in cellular signaling pathways, and is abundant in the cells of organisms where it is involved in a variety of cellular activity responses.<sup>1</sup> Previous studies have shown that the binding of allergens to the high affinity IgE receptor (FcεR1) in the mast cell line RBL-2H3 leads to tyrosine phosphorylation of the receptor  $\gamma$  subunit, thereby activating a cascade of signaling molecules, including phospholipase C (PLC), which subsequently hydrolyzes phosphatidylinositol biphosphate (PIP2) to generate IP3 and diacylglycerol.<sup>1-4</sup> The binding of IP3 to specific receptors may increase the level of intracellular calcium and cause mast cell degranulation and histamine release, thus leading to an allergic reaction.<sup>2</sup> No studies to date have explored the relationship between IP3 and the pathogenesis of chronic spontaneous urticaria (CSU), in which urticaria persists for more than 6 weeks and occurs in the absence of an identifiable provoking factor.<sup>5</sup>

Because the pathogenesis of CSU is unclear, this condition is most commonly managed in clinical practice using antihistamine therapy. In outpatient clinics, patients with chronic urticaria frequently report poor efficacy despite the use of various antihistamine drugs. The most recent urticaria treatment guidelines recommend the use of standard-dose second-generation non-sedating H1 antihistamines, and that the dosage should be increased after a maximum of 2 weeks to up to four times the standard dose.<sup>5,6</sup> In consideration of the relative differences between Asian and European populations, we used the second-generation antihistamine levocetirizine in the present study at a dose of 15 mg/day, three times the conventional dosage, and observed its efficacy and side effects in patients with CSU. Furthermore, the serum IP3 level

was determined and compared between patients before treatment and 7 days after treatment to explore the significance of IP3 in the pathogenesis of CSU.

## Materials and methods

### Study objects

All 15 patients were enrolled from outpatient clinics and met the following inclusion criteria: (i) diagnosis of CSU;<sup>6</sup> (ii) repeated use of loratadine, mizolastine, or other antihistamine and complementary medicines such as rutin and vitamin C, with limited efficacy; (iii) UAS2a score  $\geq 10$ , with UAS2a score calculated by adding the Urticaria Activity Score (UAS) on the first treatment day to the score on the day prior to treatment initiation;<sup>6,7</sup> and (iv) no glucocorticosteroid treatment within the previous month and no history of other underlying diseases or family history of genetic disease. The healthy volunteers in the control group were sex- and age-matched with the patients in the CSU group. This study was approved by the Ethics Committee of Daping Hospital, Army Medical University. Informed consent was obtained from all participants.

### Treatment and specimen collection

Samples of peripheral blood (2 mL) was obtained from patients, who were treated with oral levocetirizine 15 mg daily (Huabang Pharmaceutical), rutin 10 mg three times daily, and vitamin C 0.2 g three times daily for 7 days. UAS scores on days 7 and 8 were added and referred to as the UAS2b score, and a further 2 mL of peripheral blood was collected after 7 days of treatment. Peripheral blood samples were also collected from patients in the control group. After collection, blood samples were placed at room temperature for 2 hours and centrifuged at 1500 rpm

for 5 minutes. The resulting supernatant was stored at  $-80^{\circ}\text{C}$  until use.

### *Clinical criteria*

The treatment effect was determined using the UAS and change in wheal-and-erythema reaction or itching. The efficacy index (%) was calculated as follows:  $(\text{total score before treatment} - \text{total score after treatment}) / \text{total score before treatment} \times 100\%$ . An efficacy index  $>90\%$  was classified as recovery;  $60\%$  to  $90\%$  was highly effective;  $20\%$  to  $60\%$  was effective; and  $\leq 20\%$  was invalid. The efficiency rate was calculated as the recovery rate + highly effective rate.

### *Determination of serum IP3*

Human 1,4,5-IP3 enzyme-linked immunosorbent assay (ELISA) kits (Cusabio Technology LLC, Houston, TX, USA) were used according to the manufacturer's instructions. Curve Expert 1.3 (logistic four-parameter method) software (Cusabio Technology LLC) was used to generate curves for the determination of IP3 content in each serum sample.

### *Statistical analysis*

A paired samples t-test was used to evaluate changes within the CSU groups, and an independent samples t-test was used to evaluate differences between the CSU group and the control group. Values of  $P < 0.05$  were considered statistically significant. All analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

## **Results**

### *Effect of high-dose levocetirizine for the treatment of CSU*

In the present study, oral levocetirizine at a dose of 15 mg/day was given to the

15 patients in the CSU group for 7 days. The group consisted of 3 men and 12 women, aged from 20 to 59 years and with an average age of 37.80 years. The disease onset time ranged from 2 months to 10 years. Seven patients had an efficacy index  $>90\%$  and were therefore classified as recovered. Four of these patients showed a complete resolution of clinical symptoms (no wheal-and-erythema reaction or itching; efficacy index of 100%) and three had only occasional mild itching symptoms and no significant wheal-and-erythema reaction. A highly effective outcome was obtained in eight patients (efficacy index 72.73%–83.33%), including four cases of refractory urticaria, which had previously demonstrated unsatisfactory results despite the long-term use of conventional and alternating doses of mizolastine, loratadine, and other antihistamines. Among the eight patients with a highly effective outcome, three had mild wheals ( $<10/24$  h) and mild itching, and five had no new wheals and only mild itching. The total efficiency rate was 100%. The control group consisted of six men and nine women, aged from 18 to 47 years and with an average of 29.27 years.

### *Serum IP3 level in the CSU and healthy control groups*

In the CSU patient group, the symptoms of wheal-and-erythema reaction and itching were remarkable upon admission, the mean UAS2a score was 11.13, and the mean concentration of IP3 was  $43.54 \pm 41.97$  pg/mL. After 7 days of treatment with high-dose levocetirizine, the symptoms of skin wheal-and-erythema reaction and itching disappeared; the mean UAS2b score decreased to 1.33 and the IP3 concentration during the recovery period decreased to  $18.40 \pm 17.53$  pg/mL. The changes in UAS2a score and serum IP3 level from admission to the end of the treatment period were statistically significant

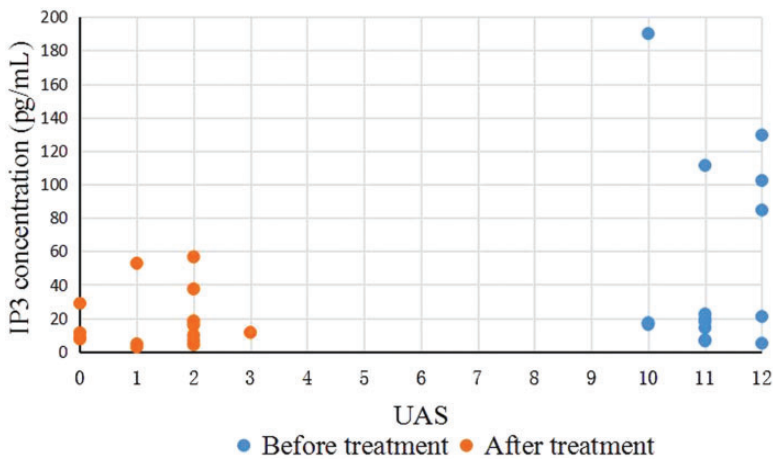
( $P < 0.05$ ). Figure 1 shows the IP3 level and change in UAS before and after treatment. A marked decrease in serum IP3 level was observed during the recovery period when compared with the onset period, indicating that IP3 may be involved in the pathogenesis of CSU.

In the healthy control group, the serum IP3 level was  $1.31 \pm 0.92$  pg/mL, which was

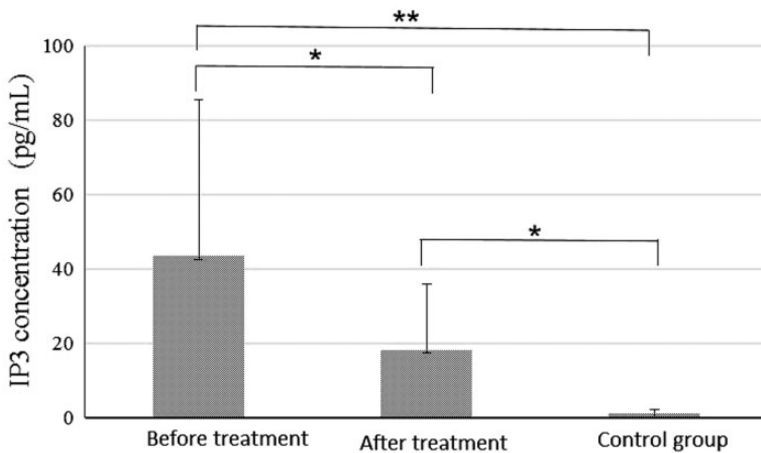
significantly lower than the levels in the CSU group before and after treatment ( $P < 0.05$ ) (Figure 2).

### Discussion

Given that the pathogenesis of CSU is unclear, current treatment for this condition remains suboptimal. The updated



**Figure 1.** Serum IP3 level and UAS score before treatment and after 7 days of high-dose oral levocetirizine treatment in patients with CSU. IPS, inositol triphosphate; UAS, Urticaria Activity Score; CSU, chronic spontaneous urticaria.



**Figure 2.** Mean serum IP3 level in the CSU and control groups. Serum IP3 level was significantly decreased at 7 days after high-dose oral levocetirizine treatment compared with before treatment in the CSU group ( $P < 0.05$ ). \* $P < 0.05$ ; \*\* $P < 0.01$ . IP3, inositol triphosphate; CSU, chronic spontaneous urticaria.

European Urticaria Guidelines recommend the use of standard doses of second-generation non-sedating H1 antihistamines for the treatment of urticaria, and that the dose can be increased after a maximum of 2 weeks to up to four times the standard dose. Moreover, higher doses do not appear to be accompanied by a corresponding increase in the incidence of adverse reactions.<sup>5,6,8</sup> In the present study, patients were administered three times the standard dose of levocetirizine for the treatment of CSU, and an effective rate of 100% was achieved after 7 days of treatment. Patients reported no significant adverse reactions, indicating the safety and efficacy of levocetirizine for the treatment of intractable CSU. In a previous study, Kameyoshi et al. used levocetirizine at a dose of 20 mg/day to effectively treat 21 patients with intractable CSU.<sup>9</sup> Siebenhaar et al. evaluated the effect of desloratadine at a dose of 5 mg/day or 20 mg/day in the treatment of acquired cold urticaria, and found that the increased dose of this antihistamine drug not only stabilized mast cells and reduced inflammatory signals but also did not increase side effects such as drowsiness.<sup>10</sup> These findings support the effectiveness of high-dose antihistamine therapy in CSU, although previous research and the present study were limited by low patient numbers, meaning that larger studies with longer durations are required to confirm these results.

The pathogenesis of CSU appears to be associated with a variety of factors such as immunity, genetics, and autoantibodies.<sup>11,12</sup> As a second messenger, IP3 is involved in signal transduction in multiple cell types, although no studies to date have examined the relationship between IP3 and urticaria. IP3 participates in mast cell degranulation processes via PLC-IP3-dependent signal transduction pathways. Heparin has been shown to be a specific blocker of the IP3 receptor, and may thus inhibit IP3-mediated calcium release within different

cells, including vascular and bronchial smooth muscle. Heparin may also inhibit allergen-induced mast cell degranulation after inhalation, thus preventing the occurrence of allergen-induced bronchial hypersensitivity reaction and skin reactions.<sup>13</sup> In the present study, changes in IP3 serum levels were evaluated during the onset and recovery stages of CSU. IP3 level was found to be significantly reduced during the recovery period, and the IP3 content was markedly higher than that in healthy participants. This finding indicates that IP3 and its serum level is closely related to urticaria, thus providing experimental evidence that IP3 plays an important role in the pathogenesis of CSU.

## Conclusion

IP3 appears to be involved in the pathogenesis of urticaria signal transduction as a second messenger, potentially leading to mast cell degranulation and histamine release. Further research is required to determine is the mechanism of IP3 generation and whether it has a role in dysregulated signal transduction pathways in the pathogenesis of CSU.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## References

1. Lee HS, Park CS, Lee YM, et al. Antigen-induced  $\text{Ca}^{2+}$  mobilization in RBL-2H3 cells: role of I(1, 4, 5)  $\text{P}_3$  and S1P and necessity of I(1, 4, 5)  $\text{P}_3$  production. *Cell Calcium* 2005; 38: 581–592.
2. Oppong E, Flink N and Cato AC. Molecular mechanisms of glucocorticoid action in mast cells. *Mol Cell Endocrinol* 2013; 380: 119–126.
3. Parravicini V, Gadina M, Kovarova M, et al. Fyn kinase initiates complementary signals required for IgE-dependent mast cell degranulation. *Nat Immunol* 2002; 3: 741–748.
4. Melendez AJ and Khaw AK. Dichotomy of  $\text{Ca}^{2+}$  signals triggered by different phospholipid pathways in antigen stimulation of human mast cells. *J Biol Chem* 2002; 277: 17255–17262.
5. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: management of urticarial. *Allergy* 2009; 64: 1417–1426.
6. Maurer M, Magerl M, Metz M, et al. Revisions to the international guidelines on the diagnosis and therapy of chronic urticaria. *J Dtsch Dermatol Ges* 2013; 11: 971–977.
7. Huang X, Li Z and Sun R. Synergistic actions of histamine-releasing factor and histamine releasing factor-reactive IgE in chronic urticaria. *Int Arch Allergy Immunol* 2017; 172: 27–32.
8. Sánchez-Borges M, Caballero-Fonseca F and Capriles-Hulett A. Treatment of recalcitrant chronic urticaria with nonsedating antihistamines: is there evidence for updosing? *J Investig Allergol Clin Immunol* 2013; 23: 141–144.
9. Kameyoshi Y, Tanaka T, Mihara S, et al. Increasing the dose of cetirizine may lead to better control of chronic idiopathic urticaria: an open study of 21 patients. *Br J Dermatol* 2007; 157: 803–804.
10. Siebenhaar F, Degener F, Zuberbier T, et al. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol* 2009; 123: 672–679.
11. Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. *Immunol Allergy Clin North Am* 2014; 34: 33–52.
12. Makris M, Maurer M and Zuberbier T. Pharmacotherapy of chronic spontaneous urticaria. *Expert Opin Pharmacother* 2013; 14: 2511–2519.
13. Jerzyńska J, Stelmach I and Kuna P. The role of heparin in allergic inflammation. *Pol Merkur Lekarski* 2000; 8: 341–346.