

Theophylline as 'Add-on' Therapy to Cetirizine in Patients with Chronic Idiopathic Urticaria

A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Key Words

Cetirizine · Inflammation · Phosphodiesterase ·
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Abstract

Background: Chronic urticaria is a prevalent condition associated with substantial disability. Its pathogenesis is not clearly understood and is divided into autoimmune and chronic idiopathic urticaria (CIU). We investigated if the non-specific phosphodiesterase inhibitor theophylline could provide additional benefit to the histamine-1 receptor (H-1R) antagonist cetirizine in CIU. **Methods:** This was a double-blind, placebo-controlled, parallel study. Patients were randomized to receive either cetirizine and theophylline (200 mg twice daily; group A, 67 subjects) or cetirizine and placebo for 6 months (group B, 67 subjects). Group A patients took theophylline for 6 more months. Response was assessed by visual analog scale (VAS) and treatment effectiveness score (TES). Blood theophylline levels were also determined at visit t = 1 and t = 7. **Results:** The study was completed by 54 of the 67 patients (80.6%) in group A and 51 of the 67 patients (76.1%) in group B. The physician VAS values

for group A were lower after t = 3, while the patient VAS values were decreased after t = 2. The physician and patient TES values in group A were statistically higher ($p < 0.05$) at all time points except for t = 1. At least 1 month of theophylline addition was necessary to obtain statistically significant benefit over cetirizine, and reducing theophylline by 50% during phase 2 did not alter this benefit. Pruritus values were reduced, but not statistically significant. **Conclusions:** Addition of theophylline to conventional H-1R antagonists was well tolerated without any adverse effects and provided considerable additional benefit in the management of CIU.

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Introduction

Chronic urticaria (CU) is generally defined as the occurrence of widespread daily or almost daily wheals for most of the week and for more than 6 weeks [1, 2]. CU represents a common disabling disorder occurring in 0.1% of the population, with an average duration of 3–5 years in adults [3].

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CU encompasses a heterogeneous group of disorders with presumably diverse etiologies. Autoantibodies directed against either the high-affinity IgE receptors (FcεRIα subunit) or IgE antibody fixed on mast cell surfaces are detected in about 20–30% of patients, thus indicating a strong autoimmune component in this subgroup [4, 5]; the remainder of the patients form the distinct group of chronic idiopathic urticaria (CIU). Histology of CU, in both subtypes, reveals a perivascular non-necrotizing infiltrate of CD4+ lymphocytes with considerable eosinophilia [6]; neutrophils, basophils and mast cells are also present [7].

Histamine-1 receptor (H-1R) antagonists are the first-choice treatment for patients with CU, but unfortunately some patients are poor responders to these agents requiring combination with a second agent [8]. More aggressive therapeutic options include low-dose alternate-day steroids or cyclosporine in severe cases [7]. Medications that might be useful as adjuvant agents include H-2R antagonists and leukotriene receptor antagonists [9]. Some anecdotal reports suggested a possible benefit of theophylline, either as monotherapy or combined with antihistamines [10].

Theophylline has been used in the treatment of asthma and chronic obstructive pulmonary disease for over 60 years and remains one of the most widely prescribed drugs for the treatment of airway diseases. In patients with mild asthma, low doses of theophylline (mean plasma concentration ~5 mg/l) reduce eosinophil numbers in bronchial biopsies and bronchoalveolar lavage [11]. Moreover, in patients with chronic obstructive pulmonary disease, theophylline reduces the total number of neutrophils and the concentration of interleukin (IL)-8 in induced sputum, suggesting that it may have anti-inflammatory actions [12]. In severe asthma, withdrawal of theophylline is associated with increased numbers of activated CD4+ cells and eosinophils in bronchial biopsies [13].

The purpose of the current study was to investigate whether addition of theophylline to the H-1R antagonist cetirizine is more effective than cetirizine alone in the treatment of CIU symptoms.

Patients and Methods

Patients

This study was performed in the Allergy Division of the 'A. Sygros' Hospital from January 2000 to December 2003 and was continued at the Division of Allergy of the 'Attikon' University Hospital from January 2004 to November 2004. Patients with clini-

cally confirmed diagnosis of CIU (with or without angioedema) were recruited. Inclusion criteria included: (1) the presence of urticarial lesions for more than 6 weeks and more than three episodes of urticaria per week; (2) symptom onset at least 12 weeks before the start of the study without any known causal food or drug allergy by positive serum skin test (autologous serum skin test), as previously described [14], in order to investigate a rather homogeneous CIU population, and (3) history of poor response to H-1R antagonists, defined as the presence of urticarial lesions more than three times per week lasting more than 2 h each time despite continuous treatment during the previous month. Exclusion criteria were: (1) the presence of physical or autoimmune urticaria; (2) urticarial vasculitis, i.e. urticaria lasted more than 24–36 h at one site [15] and subsequent blood tests showed plasma decrease in the C4 complement fraction and the presence of anti-C1q antibodies [16]; (3) pregnancy; (4) breast-feeding; (5) major systemic or psychiatric disease; (6) use of oral steroids in the month before study entry, and (7) therapy with agents that might interfere with serum levels of theophylline (carbamazepine, cimetidine, erythromycin, fluoroquinolones, isoproterenol, isoniazid, lithium, oral contraceptives, phenobarbital, phenytoin, propranolol, rifampicin and thiabendazole). Randomization of every 10 subjects meeting the previously mentioned criteria in two subgroups according to the study design was made by the computer.

Before the study commencement, the Ethics Committees of the A. Sygros and the Attikon Hospitals approved the study, and written informed consent was obtained from all study patients according to the Helsinki Declaration.

Study Design

The study was designed as a randomized, double-blind, placebo-controlled, parallel-group study. Patients were treated for 12 months in two phases and were divided into two groups. In phase 1 (6 months), group A patients (n = 67) received 10 mg of cetirizine (10 mg Zyrtec, UCB, Hellas, Athens, Greece) and 200 mg of theophylline (Theodur 200 mg, slow-release tablet, Lavipharm, Athens, Greece) daily in the morning plus 200 mg of theophylline in the evening for 6 months, and then 10 mg of cetirizine daily in the morning plus 200 mg of theophylline in the evening during phase 2 (second 6-month period) of the study. Group B patients (n = 67) were treated with 10 mg of cetirizine and placebo daily in the morning plus placebo in the evening during phase 1 and then 10 mg of cetirizine daily in the morning plus placebo in the evening during phase 2. The pharmacists of the respective hospitals prepared the specific study materials; the investigators and patients were blinded with respect to the study contents. Rescue medication was limited to loratadine tablets (Claritin, 10 mg, Shering-Plough) up to 3 per week as needed; no other medication for urticaria was permitted during the trial.

The treatment period started after the clinical diagnosis of CIU and a 2-week run-in/wash-out period, during which the patients did not receive any systemic medication (baseline visit). At the baseline visit, blood was collected from each subject to exclude any known underlying cause for hives, especially food or drug allergies. Laboratory studies included complete and differential blood cell counts, sedimentation rate, serum electrolytes, as well as renal and liver function tests. Each patient visited the department on 13 different occasions after diagnosis was made. These included an initial visit after the run-in period (t = 0) and 12 consecutive visits (t = 1–12), once monthly.

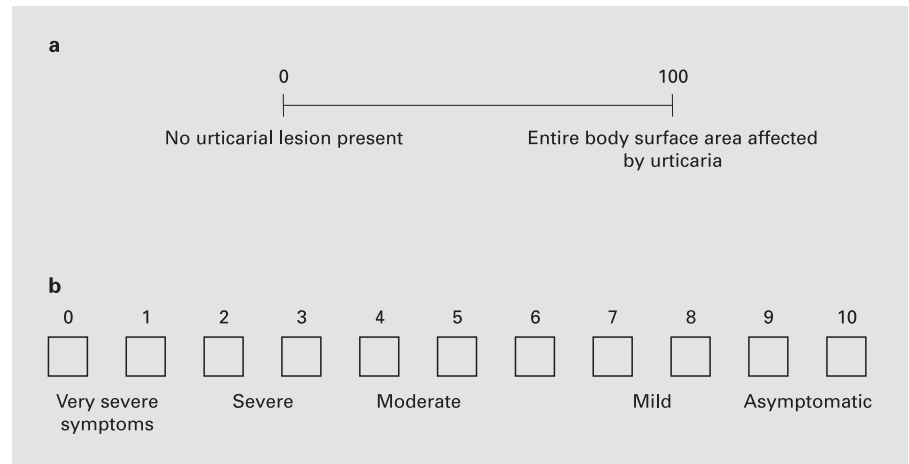


Fig. 1. **a** VAS (number and size of urticarial lesions). **b** TES (effectiveness of therapy) to monitor patient symptoms.

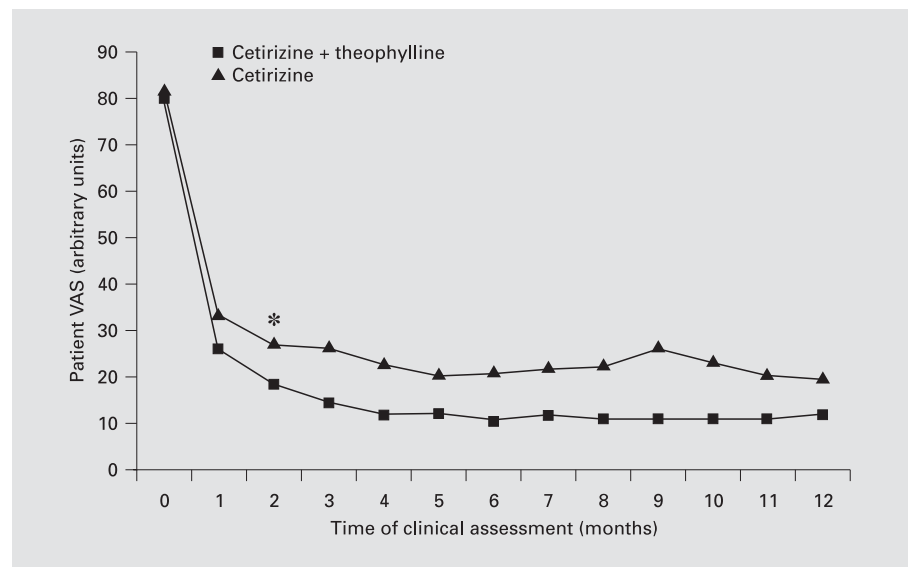
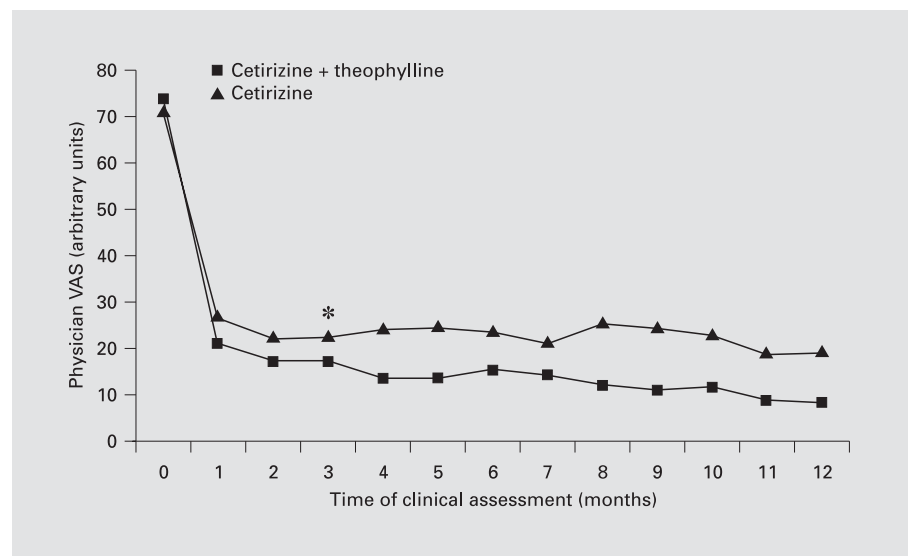
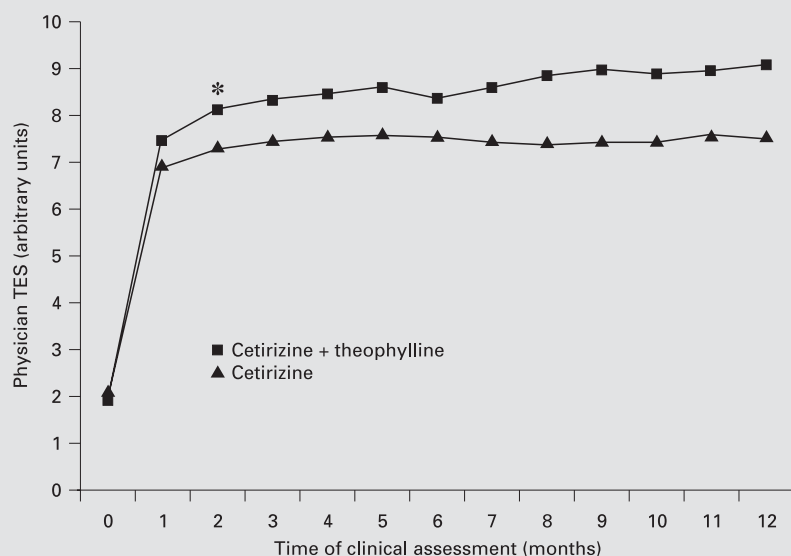


Fig. 2-5. Values for VAS (**2, 3**) and TES (**4, 5**) of the physicians (**2, 4**) and the patients (**3, 5**). Values are means (95% CI not shown). All the time points from $t = 3$ (**2**), $t = 2$ (**3**) and from $t = 1$ (**4, 5**) were statistically significant. * $p \leq 0.05$.

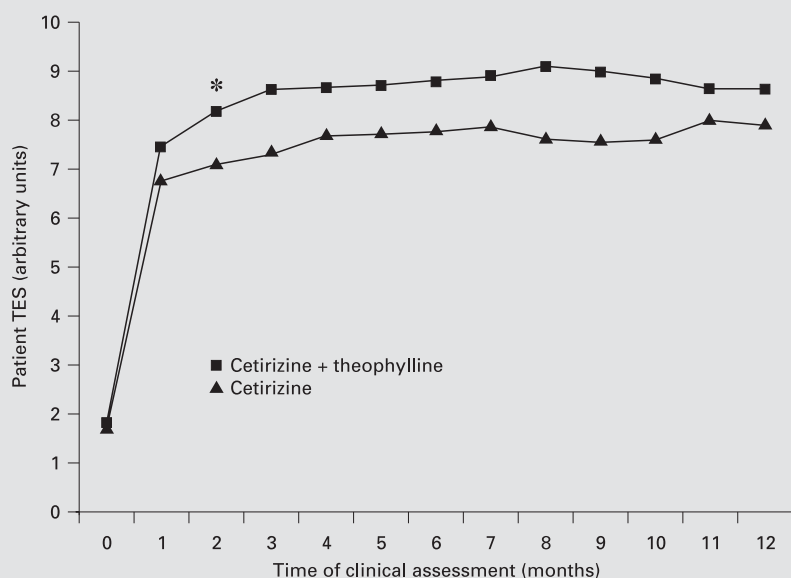
Monitoring

Both the physician and patient rated the urticarial lesions (hives) at each visit ($t = 0-12$) using two methods: (1) a 10-cm visual analog scale (VAS) and (2) an 11-point treatment effectiveness score (TES; illustrated in fig. 1). The VAS score refers to the number and size of urticarial lesions, whereas the TES reflects the effectiveness of therapy; the lower the VAS rating, the greater the reduction in urticarial lesions, conversely, the higher the TES rating, the greater the therapeutic efficacy in the entire spectrum of urticaria-related symptoms. During the 1-year study period, every effort was taken

that patients were reevaluated by the same physician. Similar approaches have been used in other clinical trials for the assessment of treatment efficacy in CIU [17–19]. Pruritus was evaluated using a 5-point scale as follows: 0 = none; 1 = minor; 2 = mild, easily tolerated; 3 = moderate, bothersome, but tolerable, and 4 = severe, almost intolerable. Moreover, at visits $t = 1$ and $t = 7$, blood was collected from each patient of group A, and theophylline concentrations in plasma were determined. The physicians were blinded to the patients who had blood drawn and to the time points of blood sampling during the study procedure.



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Table 1. Demographic data of the study population

Patient characteristics	Group A cetirizine + theophylline	Group B cetirizine
Patients, n	54	51
Sex, males/females	24/30	23/28
Mean age, years	37.0 (17–64)	39.7 (19–63)
Mean CU onset, months	25.7 (2–120)	22.6 (3–108)

No significant difference was found. Ranges are given in parentheses.

Statistical Analysis

Data are presented as means and 95% confidence intervals (CI) of the mean of the individual scores. Comparisons between the paired variables were assessed by the paired Student's *t* test. In all other cases, the results were compared using analysis of variance. Statistical significance is indicated as $p < 0.05$. The SPSS statistical package was used for analysis. There was a dropout rate of about 25%, mostly due to lack of adherence to the protocol rather than symptom worsening. Nevertheless, we did not perform an intent-to-treat analysis.

Results

Patients

One hundred and thirty-four patients were enrolled in this study. They were randomized to two treatment groups with 67 patients receiving combination therapy of cetirizine and theophylline (group A) and 67 receiving monotherapy with cetirizine (group B). Finally, 54/67 (80.6%) in group A and 51/67 (76.1%) in group B completed the study and provided the data used for statistical evaluation. Three of 16 patients in group A and 6/16 patients in group B discontinued the treatment because of symptom deterioration and unplanned use of steroids; 2 women in each group had accidental pregnancies during the study procedure and were immediately excluded. The remaining 8/13 patients in group A and 8/16 patients in group B were excluded by the investigators due to poor compliance to the study plan, although none of these subjects reported worsening of clinical symptoms.

The main demographic data of patients with respect to the baseline CIU assessment before therapy onset are presented in table 1. The mean age was 37.0 years for patients in group A and 39.7 years for those in group B; the CIU onset was 25.7 months in group A and 22.6 months in group B. There was no statistical significance between

both groups in these or any other parameters listed in table 1. The results of the VAS and TES scoring during the treatment period are presented in figures 2–5.

At $t = 1$, pruritus was 2.94 (95% CI 2.71–3.18) in group A and 2.94 (95% CI 2.70–3.18) in group B, with no significant difference compared to baseline scoring. No relapse occurred in group A during the second 6-month period ($t = 7$ –12) when the theophylline dose was reduced. However, the reduction in pruritus did not reach statistical significance.

Between both groups, the physician VAS values (fig. 2) were significant at all time points except for $t = 1$ and $t = 2$, while the patient VAS values (fig. 3) were significantly different at all time points except for $t = 1$. The TES values obtained by the physician were statistically significant between the two groups at all time points, except for $t = 1$ (fig. 4), as were those obtained by the patients (fig. 5). In patients that received the combination therapy, the mean plasma concentration of theophylline was 5.82 ± 1.58 mg/l (range 3.83–9.12) at $t = 1$ (after 1 month of treatment with 400 mg daily) and 4.77 ± 1.19 mg/l (range 2.98–7.45) at $t = 7$ (1 month after the dose reduction to 200 mg).

At least 1 month of theophylline combination treatment was necessary to obtain a statistically significant benefit over cetirizine monotherapy, and the 50% reduction in theophylline during phase 2 did not affect this apparent benefit. There were no side effects recorded following the addition of theophylline, which was well tolerated. No rescue medication (loratadine) was requested by our patients during this study.

Discussion

The present results demonstrate that the addition of theophylline significantly reduced CIU symptoms compared to the effect of cetirizine alone. Although the theophylline dose was halved after 6 months, the therapeutic benefit remained unchanged. The present study included only subjects with CIU in order to investigate a more pathogenetically homogenous population. The treatment of CU will be facilitated when it becomes more specifically tied to pathogenic mechanisms. The autologous skin test is generally accepted as the only reliable *in vivo* test for distinguishing the autoimmune subgroup of chronic urticaria; a similar study in patients with autoimmune CU would be of great interest, too. The most apparent cetirizine is a metabolite of hydroxyzine, with a good profile in CU [2, 7]. Theophylline is a non-specific phospho-

diesterase inhibitor that leads to increased intracellular cyclic AMP (cAMP) levels that may inhibit the development of hives. Interestingly, phosphodiesterase inhibitors could increase cAMP in mononuclear leukocytes from atopic, but not normal individuals [20]. However, the increase in cellular cAMP levels usually occurs in a few minutes and could not explain the need for at least 1 month of treatment before any clinical benefit was noted.

The beneficial effect of theophylline may derive from some anti-inflammatory actions [11, 21]. Theophylline inhibited for instance the proliferation of peripheral blood mononuclear cells from atopic individuals, as well as IL-4 and IL-5 secretion from Th2-like cells [22]. A phosphodiesterase-4 inhibitor blocked cytokine production from peripheral blood mononuclear cells and normal polyps [23]. Release of histamine, tumor necrosis factor- α [24] and tryptase, as well as of prostaglandin D₂ and leukotriene C₄ [25] was inhibited by β -adrenoreceptor agonists that increase cAMP from human lung mast cells, dispersed skin mast cells and human cultured mast cells.

Even though histamine plays a major role in itching associated with chronic urticaria [26], the scratching behavior of NC/Nga mice was not affected by antihistaminic agents, suggesting the involvement of other mediators [27]. Such mediators could include IL-6, IL-8, IL-13, IL-16, tumor necrosis factor- α and tryptase. Proteinase-activated receptor-2 for instance was shown to be a novel pathway for itching in human skin and was unaffected by antihistamines in atopic dermatitis patients [28]. Tryptase is known to activate this receptor in a way that

involves the peripheral nervous system [29]. Theophylline might inhibit the synthesis/release of some or all of these mediators or downregulate the expression/function of their respective receptors.

CU is commonly exacerbated by stress [30], and such patients have significantly increased expression of corticotropin-releasing hormone receptor-1 (CRH-R1), known to be released under stress, in affected skin [31]. Acute stress induces skin mast cell activation [32], mimicked by intradermal administration of CRH [33]. Mast cells are considered to play a key role in mediating the effects of stress on the skin [34] and were recently shown to express a number of CRH-R1 isoforms, activation of which led to selective release of vascular endothelial growth factor [35]. Theophylline could potentially affect the expression of other CRH-Rs that may explain why it requires 1 month before any benefit is appreciated.

A larger study where key mediators may be measured in the serum should be carried out in order to investigate the mechanism of action of theophylline in CIU. Other H-1R antagonists that also have mast cell blocking activity, such as azelastine [36] or other anti-inflammatory properties, such as rupatadine [37], may also be tested alone or in combination with theophylline or CRH-R antagonists [38].

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