

Symposium Cont.

Approach to Therapy in Chronic Urticaria: When Benadryl Is Not Enough

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ABSTRACT

Chronic urticaria is a relatively common disorder in which its management often presents a difficult clinical challenge. Histamine antagonists are the mainstays of therapy, and the second-generation antihistamines offer an attractive combination of efficacy, convenience, and lack of side effects. For patients whose symptoms are not controlled by once daily second-generation antihistamines, adjunct therapy with first generation H_1 -antihistamines, H_2 -antihistamines, doxepin, or leukotriene modifiers may be effective. Short-term systemic corticosteroids are useful for acute symptom flares but should not be used chronically. For chronically unremitting disease, immunomodulatory agents such as low-dose oral cyclosporine often are useful. (Allergy and Asthma Proc 26:9–12, 2005)

Chronic urticaria (CU) often is a debilitating disease characterized by the eruption of pruritic wheals on most days for at least 6 weeks.¹ Individual wheals usually

are transient, although regenerated such that some patients remain symptomatic on a daily basis for many years. Patients with CU often have concurrent episodic angioedema that is presumably caused by the same underlying process. In recent years, it has been shown that up to 50% of patients with CU have functional autoantibodies directed against the α -chain of the high-affinity immunoglobulin E receptor,² and these patients may be identified by skin testing with autologous serum. However, an identifiable cause for CU often is not apparent after a thorough history, physical examination, and appropriate diagnostic tests. Despite not understanding the cause of CU in many cases, we do have knowledge of its natural history. CU tends to have a relapsing course, with some patients experiencing severe, episodic, acute episodes of urticaria and angioedema requiring urgent medical treatment. In others, the disease has a relatively constant baseline symptomatology that is controllable with safe and effective therapy. The average duration of the disease is 3–5 years, although some patients continue to experience symptoms for ≥ 20 years.³

Physical urticaria often accompanies CU, including delayed pressure urticaria. Identifying delayed pressure urticaria has important treatment implications because often it does not respond well to antihistamine therapy.⁴ Another possible concurrent physical urticaria that might alter CU treatment recommendations is exercise-induced anaphylaxis (EIA). EIA patients experience acute worsening of their symptoms during exercise, and in a significant subset of these patients the exercise only provokes symptoms if they have eaten a specific food (identifiable by skin testing) within several hours.⁴ Some food-dependent EIA patients experience symptoms when they exercise after eating regardless of the food eaten.

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There are several patient education issues to address with CU patients that may help alleviate symptoms and reduce their need for pharmacotherapy. These include avoidance of exacerbating factors such as exposure to certain medications, alcoholic beverages, heat, and overtiredness.¹ The medications most often implicated are the nonsteroidal anti-inflammatory drugs (NSAIDs). Although these agents are known to occasionally cause acute anaphylactoid reactions (and therefore patients present with an awareness of the culprit), in the majority of cases of CU the hives will simply be worse on days when these agents have been taken and, therefore, the NSAID contribution to symptoms is not recognized. CU symptoms also may be exacerbated by angiotensinogen-converting enzyme inhibitors, and, therefore, some consideration should be given for substituting a different class of medication.

Despite the importance of addressing concurrent diagnoses and general patient education regarding factors that tend to exacerbate urticaria, the mainstay of therapy for CU is pharmacotherapy. The remainder of this review will be devoted to a discussion of the different medications that have been used for treating CU. These include agents that block the actions of relevant chemical mediators such as histamine (H_1 -antagonists, H_2 -antagonists, and the tricyclic antidepressant doxepin) and the leukotrienes (montelukast and zafirlukast) and agents that act to prevent or at least temporarily interrupt the process that results in histamine release (immunomodulatory agents).

H_1 -ANTAGONISTS

Antihistamines selective for the H_1 -receptor are the mainstays of CU pharmacotherapy. The so-called "first-generation" antihistamines traditionally have been the first-line of treatment, and these include agents such as hydroxyzine, diphenhydramine, and chlorpheniramine. Although effective in alleviating urticarial symptoms in many patients, two significant drawbacks have plagued these first-generation agents: a requirement for dosing multiple times each day (to achieve maximal control of symptoms) and inherent sedative effects.

The introduction of second-generation H_1 -receptor antagonists was an important advance in the treatment of urticaria, allergic rhinitis, and allergic conjunctivitis. Terfenadine and astemizole were the initial second-generation agents to receive Federal Drug Administration (FDA) approval in the United States, although both have been since removed from the market because of their potential to prolong the QT interval at high serum levels. This complication was seen most often when these agents were administered concurrently with erythromycin, ketoconazole, or another medication metabolized by the same hepatic cytochrome P_{450} enzyme. None of the currently available second-generation agents share the same metabolic pathway, nor have they been observed to increase the risk of cardiac arrhythmias. The currently available agents include lorata-

dine, cetirizine, fexofenadine, and desloratadine. Each of these agents has received FDA approval for once-daily dosing, and as a group they are much less sedating than the first-generation agents.

A variety of controlled trials have evaluated the efficacy of second-generation antihistamines for the treatment of CU, including several that included the first-generation agent hydroxyzine as an active comparator. Both cetirizine⁵ (5–20 mg daily) and loratadine⁶ (10 mg daily) have been shown to result in equivalent efficacy and less sedation than hydroxyzine (25–75 mg three times per day). Neither fexofenadine nor desloratadine have been compared directly with hydroxyzine in CU, although controlled studies involving their parent compounds (terfenadine and loratadine, respectively) report efficacy equivalent to hydroxyzine.^{6,7} Fexofenadine versus placebo has been studied extensively,^{8–10} including two studies assessing multiple doses of fexofenadine.^{8,10} Doses of 60, 120, and 240 mg twice daily were each shown to have greater efficacy than either 20 mg twice daily or placebo. There was no clear dose response beyond 60 mg twice daily in either study.

Although the efficacy of the various second-generation antihistamines in CU appears to be comparable, the safety profiles of these agents differ. According to the package inserts, cetirizine is sedating and loratadine, fexofenadine, and desloratadine are "nonsedating" at the recommended doses. Indeed, dose-dependent cognitive and psychomotor impairment has been shown with cetirizine. However, in the CU trial comparing cetirizine with hydroxyzine, hydroxyzine, but not cetirizine, was more likely than placebo to result in sedation.⁵ Loratadine and desloratadine are nonsedating at their approved doses but appear to exhibit dose-dependent sedation at higher doses. Fexofenadine is the only available agent that does not appear to have the capacity to cause sedation, even at 240 mg twice daily.

There is a discrepancy between the approved dose of antihistamine agents and the commonly prescribed dose. An informal poll of allergists in attendance at this conference revealed that nearly every attendee routinely prescribes higher than approved doses of antihistamines for their urticaria patients. This suggests that among allergy specialists the "standard of care" for treating this relatively common disease state has not been studied adequately enough to obtain the FDA's endorsement. Although this may reflect an endemic overzealous and costly practice style, it also is possible that urticaria subjects included in published clinical trials are not representative of those who are seen in clinical practice by allergy specialists. It may be that there are subgroups of patients (*e.g.*, more severe patients) who respond to a higher-dose antihistamine therapy.

H_2 -ANTAGONISTS

Cutaneous blood vessels possess histamine receptors of both the H_1 (85%) and H_2 (15%) subtypes, and both are involved in the mediation of cutaneous vasodilatation

and vascular permeability. Clinical studies using combined H₁- and H₂- antihistamines (cimetidine and ranitidine) in CU generally have shown an augmentation of the effect of an H₁ blockade alone, although the clinical improvement generally is modest.^{11–13} Because H₂-antihistamines generally are safe and inexpensive, and because individual patients may exhibit significant responses, a trial of an H₂-antihistamine (such as ranitidine 150 mg three times per day) added to an H₁-antihistamine is reasonable for patients who have not responded adequately to an H₁-antihistamine alone.

TRICYCLIC ANTIDEPRESSANTS (DOXEPIN)

Doxepin is a tricyclic antidepressant and a potent inhibitor of both H₁- and H₂-receptors. It is approved for the treatment of depression in doses of up to 300 mg per day and has been shown to be more effective than diphenhydramine in controlling urticaria.^{14–15} Unfortunately, doxepin is highly sedating and often results in anticholinergic side effects. The gradual increase in a bedtime dose (*e.g.*, 10–25 mg for 1–2 weeks and increasing to 50 mg) reduces side effects and often is a useful adjunct to H₁-antihistamine therapy.

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroid treatment (*e.g.*, prednisolone and methylprednisolone) is effective for acute urticaria and CU,¹⁶ although long-term treatment with these agents for CU is contraindicated because of inevitable side effects associated with their long-term use. A reasonable course might consist of a single daily dose of prednisone, 40 mg, for 3–5 days with a subsequent taper over 7–10 days.¹⁷

LEUKOTRIENE MODIFIERS

The leukotrienes may have a role in the pathophysiology of CU because they are synthesized by mast cells and have local effects on the cutaneous vasculature. To establish whether leukotriene modifiers have a role in the treatment of CU, there have been multiple uncontrolled^{18,19} and controlled^{20–23} trials of these agents used in combination with antihistamines. These studies generally have shown modest²⁰ or no²¹ benefit compared with antihistamine treatment alone, although subsets of patients appear to improve significantly when these agents are added. Given these data and the relative safety of montelukast and zafirlukast, if antihistamine therapy alone is not controlling CU symptoms, it is reasonable to add one of these agents for 2–4 weeks on a trial basis.

IMMUNOMODULATORY AGENTS

A variety of immunomodulatory agents have been used in the treatment of CU when antihistamine treatment fails to control symptoms. These include sulfasalazine,²⁴ dapsone,²⁵ colchicine,²⁶ methotrexate,²⁷ cyclosporine,²⁸ plasmapheresis,²⁹ and intravenous immunoglobulin.³⁰ Of

these, low-dose cyclosporine has received the most attention recently, particularly in the subset of CU that is associated with autoimmune disease. In one randomized, double-blind study, 30 autologous serum skin test-positive adults with CU were randomized to cetirizine (10 mg daily) plus either cyclosporine (4 mg/kg per day) or placebo.²⁸ Roughly one-half of the patients who received cyclosporine responded. For refractory CU patients with a positive skin test to autologous serum, a 1- to 3-month trial of cyclosporine (2.5–4.5 mg/kg per day) is reasonable. Relapses are common, although they tend to be less severe. Given the potential of cyclosporine to cause renal toxicity, it is important to monitor renal function during treatment.

SUMMARY AND CONCLUSIONS

CU is a potentially debilitating disease in which its cause often is not identifiable. The principals of CU treatment include educating patients regarding avoidance of exacerbating factors (such as overtiredness, alcohol, and NSAIDs) and medications to control symptoms while minimizing side effects. Antihistamines are the mainstay of the pharmacotherapy of CU, and the second-generation H₁-antihistamines have had an enormous impact on outcomes by virtue of their efficacy, long half-lives, and relative lack of side effects when compared with the first-generation agents. It is of interest that practicing allergists (including this author) routinely prescribe antihistamines in excess of the approved doses for CU and that dose-ranging studies, to date, have not shown a dose response at these higher doses. H₂-antihistamines, leukotriene modifiers, and doxepin are useful long-term adjuncts to H₁-antihistamines in selected patients. Systemic corticosteroids, although usually very effective, should be reserved for short-term rescue during severe flares. Refractory CU cases usually remit when treated with a combination of antihistamine therapy and an immunomodulatory agent such as cyclosporine.

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