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CLINICAL TRIAL REPORT

Treatment of Cold Urticaria

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Trial

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.

Rating

••Of major importance.

Introduction

Acquired cold urticaria is a chronic physical urticaria characterized by wheals in response to exposure to cold temperatures. Therapy is dependent on antihistaminics, yet patients with severe symptoms may be unresponsive to doses of second-generation antihistamines, which are typically used to treat allergic rhinitis. One approach that has been used successfully for more than 30 years is to prescribe four to eight tablets of cyproheptadine daily. However, side effects of somnolence and increased appetite can be limiting.

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Aims

To assess a high dose of a second-generation (relatively nonsedating) antihistamine as treatment for cold urticaria.

Methods

A double-blind, randomized, placebo-controlled, crossover study compared the efficacy and safety of desloratadine, 5 or 20 mg, or placebo, each administered once daily for 7 days, among patients with acquired cold urticaria. An acquired cold urticaria severity index was used to describe the baseline characteristics of the patients. At screening, a positive cold provocation test for 10 min at 4°C was required for eligibility. Patients were randomly assigned with six possible sequences of placebo or low- or high-dose desloratadine. Each 7-day treatment period was followed by a 14-day washout period before crossover to the next treatment group. Cold provocation tests employed plastic-embedded thermoelectric elements with a thermal range of 0°C to 42°C and were performed at the end of each 7-day treatment period. The wheal and flare reaction was then analyzed by digital, three-dimensional, time-lapse photography and thermographic imaging. A critical temperature threshold was determined to be the shortest time needed to induce wheal development by a cold provocation at 4°C, and the shortest duration of application time required for wheal development was noted. Symptom scores were determined at 10 min after introduction of the cold stimulus. A total of 30 patients with cold urticaria were studied.

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Results

Although 5 mg of desloratidine for 7 days was more effective than placebo, the 20-mg dose was a significant improvement over the 5-mg dose. The critical temperature threshold was superior with the higher desloratidine dose, and both doses of desloratadine improved patient symptoms, although only the higher dose significantly affected pruritus. A total of 15 patients treated with 20-mg desloratidine reported complete protection from a cold challenge, 7 patients responded similarly with 5-mg desloratadine (making for a total of 22 of 30), while only one of 30 patients treated with placebo had a negative challenge. Side effects were minimal, and somnolence was not reported.

Discussion

Treatment of physical urticarias with antihistaminics has been an important step in approaching the utility of these agents in more complex urticarial disorders such as chronic urticaria (idiopathic or autoimmune) because these physically induced hives lack a late-phase component and are largely—if not exclusively—histamine mediated. Although double-blind, placebo-controlled studies have not been done, it has been clear for the past 35 years that the dose of first-generation antihistamines would have to be raised considerably to treat patients with severe urticaria symptoms. Thus, cyproheptadine, the antihistamine of choice for cold urticaria for many years, could be administered in the 4- to 8-tablet/d dose range with not only amelioration of symptoms but conversion of the ice cube cold challenge test to negative in most patients. This new study using desloratadine is important because 1) it was properly controlled, 2) it used very sophisticated methodology in assessing the severity of cold urticaria, and 3) the result was very promising (ie, successful employment of increased amounts of a second-generation antihistaminic with a much improved side effect profile compared with first-generation agents).

Comments

As desloratadine (5 mg) is somewhat less effective for inhibition of histamine-induced wheals when compared with cetirizine (10 mg), desloratadine or alternative antihistaminics may be tried in doses of 3 or 4 tablets/d (based on this study) and perhaps raised to even 6 to 8 tablets/d for the small minority of patients who are not sufficiently responsive to 4 tablets/d. This study also suggests that a similar approach may be tried, not only with other physical urticarias (except perhaps delayed-pressure urticaria) but also with chronic urticarias that are considered idiopathic or autoimmune.

Disclosure Dr. Kaplan has served as a consultant for Novartis and Sanofi-Aventis and on the speakers' bureau for ViroPharma, Dyax Corp., Shire, and GlaxoSmithKline.