

The clinical efficacy of antihistamines in the skin

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Introduction

Chronic idiopathic urticaria represents a distressing and troublesome clinical condition, the cause of which remains unidentified in up to 90% of patients. There is a clear need for improved medications for the symptomatic treatment of this disorder, since the underlying cause remains unknown. To date, however, antihistamines remain the mainstay of therapy. This review will focus on the six Cs of antihistamine treatment: convenience, cure, complications, caution (drug interactions), cost, and comprehensiveness, a list which has been adopted from a similar approach described for antifungal agents (1). It is hoped that such an approach will permit an evaluation of the utility and versatility of antihistamines and allow one to decide which of the medications in this class has the most to offer for treatment of urticaria.

Convenience

Antihistamines are best tolerated when they cause little, if any, drowsiness. From a clinical standpoint, it is a great advantage if a medication can be taken once or twice daily, as it is then much more likely that the patient will continue with the treatment. There is good evidence that the first-generation antihistamines are very effective for patients with chronic urticaria. However, it is recognized that these agents are not well tolerated because of their short half-lives, resulting in more frequent dosing and greater sedative effects. Despite the disadvantages of the first-generation antihistamines, they are frequently used by many dermatologists, since the knowledge and understanding of second-generation antihistamines is still evolving in the specialty. The currently available second-generation

antihistamines include acrivastine, astemizole, azelastine, cetirizine, ebastine, epinastine, fexofenadine, levocabastine, loratadine, mizolastine, oxatomide, and terfenadine. Several of these agents are in general use in the USA, but, because of their cardiac side-effects, terfenadine and astemizole are no longer available. Terfenadine has recently been replaced by its metabolite fexofenadine. At present, fexofenadine is not indicated for the treatment of urticaria in the USA; thus, few dermatologists have information about this antihistamine. While at first glance there appear to be few differences among second-generation antihistamines, in reality they have very different chemical structures (2), along with variations in therapeutic profiles, side-effects, half-lives, tissue distribution, metabolism, and degrees of antiallergic effects. Thus, with the passage of time, it has become apparent that the newer antihistamines in fact represent a heterogeneous group of compounds.

Similarly, it is important to recognize that urticaria is a cutaneous reaction pattern of which there are numerous clinical presentations and possible causes. In other words, it is a heterogeneous disorder. The most common type of chronic urticaria is the idiopathic followed by urticaria with physical causes such as mechanical trauma, light, heat, cold, or water. Occult infections, contactants, food, and food additives are much rarer causes of chronic urticaria. It is also important to remember that there are some systemic diseases which present as urticaria-like lesions. These include thyroid disease, systemic lupus erythematosus, pruritis, urticarial papules and plaques of pregnancy, neoplasms, and mastocytosis (3).

The second-generation antihistamines have been widely used in the treatment of the various forms of urticaria. While some patients with chronic urticaria

benefit from treatment with these medications, not all respond (4–7). This is due to various reasons, including the fact that the cure of urticaria remains the identification and elimination of the cause. In addition, mast-cell mediators other than histamine are likely to play a role in some forms of urticaria. Of the second-generation antihistamines, cetirizine and terfenadine have proven to be the most effective. We have just completed a double-blind, placebo-controlled study comparing loratadine with cetirizine in patients with chronic idiopathic urticaria (data on file, Pfizer). However, the results from this study, together with our clinical experience in the USA, show that loratadine is not a very good antiurticarial drug.

There is strong evidence that patients with chronic urticaria can be divided into two groups: those who respond to antihistamines and those who are relatively resistant. We believe that the majority (80–90%) of patients who respond to antihistamines have a lymphocyte-predominant inflammatory cell infiltrate in lesional skin; we have termed their disorder lymphocyte-predominant urticaria (LPU). The second group of urticaria patients who are relatively resistant to antihistamine therapy frequently have a predominance of neutrophils and eosinophils in lesional skin, and this form of the disease has been labeled polymorphonuclear cell-predominant urticaria (PPU) (8). It is well known that the introduction of an allergen into the skin of a sensitized patient results in an immediate wheal-and-flare reaction with many similarities to the lesions seen in urticaria. In certain instances, this reaction may be followed 2–8 h later by the development of an erythematous, indurated area at the site of the allergen introduction. This cutaneous response has been termed the late-phase reaction. The cutaneous cellular infiltrate at the time of this reaction contains predominantly neutrophils and eosinophils, which are replaced by a mononuclear cell infiltrate 24–48 h later. We have proposed that patients with chronic PPU have cellular infiltrates very similar to the early component of the late-phase reaction. Clinically, LPU and PPU patients differ in the fact that the lesions of LPU itch, whereas PPU lesions have a tendency to burn and sting as much as itch. Generally, the individual lesions of LPU last less than 24 h, whereas PPU lesions often persist for longer than 24 h.

Cure

The true cure for patients with chronic urticaria is the identification and elimination of the cause. However, this may be possible in as few as 10–20% of patients. Thus, in the remaining patients with disorders for which no cause can be identified, and lymphocytes are the predominant inflammatory cell infiltrate, antihistamines appear to be the treatment of choice. This

indicates an important role for histamine in this patient group.

A number of studies have compared different antihistamines for their efficacy in the treatment of urticaria. One compared cetirizine (5, 10, or 20 mg) with its parent compound hydroxyzine (25, 50, or 75 mg) and placebo in a blinded protocol (4). Cetirizine was delivered just once a day along with two placebo tablets, while hydroxyzine was given up to three times a day. The patients were started on the lower dose of each drug; that is, 5 mg for cetirizine and 25 mg for hydroxyzine. They were allowed to increase to 10 or 20 mg of cetirizine or 50 or 75 mg of hydroxyzine per day if no benefit was obtained from the starting dose. Cetirizine was shown to be as effective as hydroxyzine in terms of the clinical effect on number of lesions and intensity of pruritus. Of interest was the finding that nearly 40% of the patients required a dose of 20 mg of cetirizine to control their symptoms. A double-blind, placebo-controlled study compared cetirizine with astemizole for 4 weeks of therapy in patients with chronic idiopathic urticaria. Cetirizine was superior to astemizole during the first week, after which the drugs had comparable efficacy. Both drugs were well tolerated, but clinical benefit occurred more rapidly with cetirizine (9). Terfenadine and cetirizine were compared for their effectiveness in chronic urticaria patients. By 10 days, both agents significantly decreased the number of wheals and associated erythema. The global assessment showed cetirizine to be somewhat superior to terfenadine after 10 and 20 days of treatment, but both agents proved to be very effective in controlling the patients' signs and symptoms (10). A number of other studies have confirmed the usefulness of cetirizine, compared with other second-generation antihistamines, in the treatment of chronic urticaria (11–13).

Complications

While second-generation antihistamines have proven to be effective in the treatment of chronic idiopathic urticaria, side-effects, or "complications", have occurred with their use (4, 5, 7, 10). However, second-generation histamine antagonists cause less sedation, fatigue, and dry mouth than first-generation antihistamines and thus are better accepted by patients with chronic disease. Of loratadine, fexofenadine, and cetirizine, the last appears to cause the most sedation. While, at first glance, this may appear to place cetirizine at a disadvantage compared to the other second-generation antihistamines, dermatologists actually utilize cetirizine's sedative properties to facilitate sleep for patients who have pruritic skin disorders.

Overall, when compared to first-generation antihistamines, cetirizine, loratadine, and fexofenadine

essentially have no “complications”. The superiority of these antihistamines to first-generation agents is supported by a number of studies showing that very few patients discontinued these medications as a result of adverse events (4, 6, 7, 10). Therefore, it can be assumed that the therapeutic benefits of these second-generation antihistamines greatly outweigh any side-effects.

Caution: drug interactions

Recently, the focus on the risk/benefit ratio of antihistamines has shifted from sedation to the potential to cause serious ventricular arrhythmias of the torsade de pointes type, which was first reported with astemizole and later with terfenadine (14, 15). Reports indicate that the concomitant use of ketoconazole, itraconazole, quinine, and erythromycin can elevate levels of these antihistamines, thus putting patients at risk of life-threatening cardiac arrhythmias. The possibility that such cardiotoxicity was a side-effect common to all second-generation antihistamines has been discounted since cetirizine, loratadine, and fexofenadine have not been associated with adverse cardiovascular effects. Because cetirizine and fexofenadine are metabolites of the parent compounds hydroxyzine and terfenadine, respectively, they do not undergo significant hepatic metabolism, and are thus less likely to be involved in adverse drug–drug interactions.

Cost

Second-generation antihistamines are more expensive than first-generation agents. Among the second-generation histamine antagonists, there is little difference in cost. In the USA, medication costs are a growing concern of health-care companies and patients; as a result, there is pressure on physicians to use the less expensive (often generic) medications. However, physicians must resist this pressure and consider the issues of safety and efficacy, together with patient compliance, as their main concern. It is clear that if a less expensive medication has a greater side-effect or is less efficacious, its therapeutic value is diminished. Therefore, the true costs of using cheaper but inadequate medications must be impressed on health organizations in the USA and elsewhere.

Comprehensiveness

Although the ability of antihistamines to exert anti-allergic effects in man has been appreciated for some time (16), the question of whether this enhances their therapeutic benefit has been the subject of much debate. Of the currently available second-generation antihista-

mines, it appears that cetirizine has by far the most documented antiallergic effects (17). Recent studies suggest that cetirizine may be effective in diminishing the late-phase reaction (18–20). In atopic patients, eosinophils and other cells are attracted by intradermal injection of allergen or platelet-activating factor. The accumulating cells can be identified and counted by the skin-window technique or cutaneous punch biopsies. By the skin-window method, Fadel et al. demonstrated inhibition of eosinophil accumulation by cetirizine at skin sites challenged with pollen (18) or platelet-activating factor (19). The findings with allergen-induced, late-phase cutaneous responses were confirmed by Charlesworth et al. in a double-blind, placebo-controlled, crossover study in which cetirizine decreased eosinophil infiltration into skin blisters by approximately 80% in ragweed-sensitive subjects. This effect could not be attributed to cetirizine's H₁ activity since cetirizine did not block histamine-induced eosinophil infiltration. Furthermore, two potent first-generation compounds, chlorpheniramine and promethazine, had no inhibitory effect on eosinophil migration (20).

Should cetirizine be shown to have true clinical efficacy in inhibiting the migration of eosinophils and neutrophils in the skin, it could prove to be highly desirable in the treatment of a number of cutaneous diseases. While it is effective in the treatment of LPU, cetirizine may also prove efficacious in the management of PPU. Patients with chronic PPU respond poorly to antihistamines alone and frequently require the addition of colchicine or dapsone, both of which have anti-polymorphonuclear cell effects (8). The ability of cetirizine to diminish the accumulation of eosinophils in the skin of atopic dermatitis patients, in which eosinophils and their granule mediators are a prominent feature, could be of great value in managing this disease (21). Several studies have reported cetirizine to be useful in the treatment of atopic dermatitis. In one such study (22), 127 atopic dermatitis patients were treated for 4 weeks with cetirizine (10, 20, or 40 mg) or placebo. Compared with placebo, pruritus was significantly reduced in patients receiving 20 and 40 mg cetirizine, and those receiving 40 mg/day also experienced a reduction in erythema, lichenification, lesion size, and total symptom score. Both patients and investigators expressed a preference for cetirizine 40 mg/day over the lower doses or placebo. While sedation increased with dosage, it was felt by the investigators that the extent of improvement was greater than the degree of sedation. It is possible that the improvement of skin lesions might have occurred in part through cetirizine's anti-inflammatory properties.

There are a number of cutaneous disorders in which either eosinophils or neutrophils predominate, such as bullous pemphigoid, dermatitis herpetiformis, pemphigus vulgaris, linear IgA bullous dermatosis, subcorneal pustular dermatosis, granuloma faciale, and pyoderma

gangrenosum, to name a few (23). Recently, we have begun to use cetirizine (20 mg b.i.d.) as a corticosteroid-sparing agent in bullous pemphigoid patients whose corticosteroid dose we were unable to reduce. In two such patients, the addition of cetirizine has permitted the tapering of the corticosteroids to lower levels while maintaining the patient lesion-free.

Conclusion

In summary, with the exception of cost, cetirizine, loratadine, and fexofenadine have many advantages over their predecessors in convenience and compliance, cure, complications, caution, and comprehensiveness. Because cetirizine and fexofenadine are metabolites of their parent compounds and thus do not undergo liver metabolism, they are less likely to interfere with other medications. The observation that cetirizine may possess important anti-inflammatory, as well as anti-histamine, activities suggests that it may be useful in the treatment of a number of inflammatory skin diseases. Future studies should help to define the role of this medication, as well as those of other second-generation antihistamines, in the treatment of dermatologic diseases.

Discussion

De Vos: I don't remember seeing such a high level of headache reported for cetirizine. You quoted 14%. Is that taken from the package insert?

Tharp: Yes, this information is from the package insert for pediatric patients, aged 6–11 years.

De Vos: What were the levels of headache for the placebo?

Tharp: All the data that I presented are from studies performed in the USA. The incidence of headache in the placebo group was 12.3%, for 5 mg of cetirizine 11%, and for 10 mg of cetirizine 14%.

De Vos: These data contradict a study by Meltzer (24). Although it is the only one we have available for comment, it was done on 24 patients. It compared cetirizine with loratadine and showed that, in this study at least, loratadine had a very high incidence of headache versus cetirizine and placebo.

Tharp: Considering that the placebo group had a 12.3% incidence of headache in this pediatric population, I do not think that 14% is very high.

De Vos: Do you think that it is possible to have different profiles of adverse events in different medical conditions?

Tharp: Yes, I think that is possible.

Timmerman: If you can see differences in efficacy between people with a disease and normal individuals, it would be expected to be the same for side-effects.

Tharp: There are many things that can affect a patient's perception of symptoms like pruritus or somnolence or maybe even headache. We all have different itch and pain thresholds which can be affected by a number of factors such as time of day, sleep deprivation, mood, etc.

De Vos: You mentioned that fexofenadine is given twice a day; that is true only in the USA. In the rest of the world, the medication is given at 120 mg per day for seasonal allergic rhinitis, and in some countries fexofenadine is approved for chronic idiopathic urticaria at 180 mg per day in one tablet. I would like to ask you for your feelings about these higher dosages for chronic idiopathic urticaria versus seasonal allergic rhinitis for fexofenadine. Second, is it necessary to give a higher dosage of fexofenadine than the corresponding terfenadine treatment in chronic idiopathic urticaria?

Tharp: I believe cetirizine is a much more effective agent for urticaria given as a twice-a-day dose. This is supported in part by the fact that its half-life is 10–14 h. I believe the same is true for loratadine. In a clinical situation such as urticaria, it is not a problem for patients to take a medication twice a day if it is providing relief, and I believe the divided dosage gives more consistent blood levels and a better therapeutic response. While I have not used fexofenadine, my impression is to divide this dose as well, given its half-life. It is also possible that a higher dose of 180 mg might be necessary for the treatment of hives, whereas 120 mg might be adequate for allergic rhinitis. From what I have read, I believe that fexofenadine might be similar to loratadine in terms of its efficacy in the skin. Do you have any information about this?

De Vos: Yes, a recent study emphasizes the potential differences between members of the second-generation class of drugs. This double-blind, crossover study compared cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine with placebo for suppression of the histamine-induced wheal and flare. Epinastine had the most rapid onset of action, followed by cetirizine, while terfenadine induced a potent inhibition which was superior to its metabolite fexofenadine. The rank order of inhibitory effect was cetirizine, epinastine, terfenadine, ebastine, fexofenadine, loratadine, and placebo. Thirteen out of 14 subjects showed greater than 95% inhibition of wheal area by cetirizine; just 6/14 had a similar response after treatment with terfenadine, epinastine, and ebastine; 5/14 after fexofenadine; and 2/14 after loratadine (25).

Tharp: This brings up an interesting question: why is it that loratadine, for example, seems to be less potent in the skin than in the nose? There may be a number of explanations, including its ability to reach the skin, or perhaps the way that it binds to the histamine receptors in different tissues. It might be possible that at a dose of 10 mg/day there may be insufficient concentrations of loratadine to affect enough histamine receptors in the

skin – remember the skin is the largest organ in the body and has a great number of histamine receptors. While I am unsure of the mechanism, I strongly believe that different second-generation antihistamines have varying degrees of potencies in the skin.

De Vos: Fexofenadine's bioavailability is very poor, and there appears to be a problem of absorption of the drug. In the study I mentioned, we saw better consistency of results with cetirizine and terfenadine than with the other H₁ antagonists. In patients or volunteers, cetirizine gave more than 95% inhibition of the wheal and flare, while for fexofenadine it was half this, so it's probably a problem of absorption.

Tharp: It could be.

De Vos: You mentioned that loratadine seems to be better in the nose than in the skin. But if you give a very strong nasal challenge, loratadine seems to be not so efficacious. We are about to publish studies which used an environmental unit, showing a clear-cut difference between placebo and cetirizine or loratadine in a controlled situation. However, when the magnitude of the challenge was increased, with a lot of pollen in the air, it seems that cetirizine was able to control the resultant symptoms while loratadine could not.

Sake: I have a short comment. At the last American Academy meeting, Estelle Simons presented new, unpublished data where she repeated the trial she conducted a number of years ago but with a number of new products which were not available on the US market at the time of the original trial. She in fact confirmed all her previous findings. Data on loratadine, cetirizine, and terfenadine inhibition of histamine-induced wheal and flare were superimposable on those from her previous study, but fexofenadine clearly had much less activity than terfenadine, being very similar to that of loratadine.

Timmerman: At this stage, I would like to ask whether \$2 a day is really expensive when you compare this with what it costs when people are not able to go to their jobs.

Taglialatela: One short question: have all these anti-inflammatory properties of H₁ receptor antagonists been tested preclinically or in animal models of inflammation?

Walsh: There are several animal models: for example, cetirizine reduced eosinophilia in bronchially challenged monkeys (26), it reduced the ovalbumin- (27) or PAF (28)-induced eosinophilia in the rat pleural cavity, and it also reduced Ag-induced eosinophil influx into the trachea of dogs (29). Mizolastine inhibited arachadonic acid-induced paw inflammation (30) and colitis in rats (31), and neutrophil and eosinophil migration in antigen-challenged guinea pigs (32).

Rihoux: There are many *in vitro* studies on isolated cells and tissues, but not so many using animals, as we realized early on that cetirizine was not very effective in experimental animal models.

De Vos: The problem with cetirizine in murine models, especially in the rat, is that it is metabolized so that it's no longer cetirizine. The metabolic profile of cetirizine in dogs, monkeys, and man is completely different from the murine species, so it's difficult to compare. Therefore, data from murine animal models are not really very useful.

Timmerman: This is an important point, Christine [De Vos]. What is the difference between species that allow the metabolism of cetirizine? This could provide interesting answers which could be used in drug design.

Tharp: From the skin standpoint, there, unfortunately, is no good animal model for either urticaria or atopic dermatitis, so man becomes the model.

De Vos: Yes, it's the same for asthma.

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