Dermatologists have adopted antihistamines into practice to manage a variety of conditions, the most common of which are chronic idiopathic urticaria (CIU) and pruritus (often associated with atopic dermatitis). In fact, antihistamines are said to rank with antibiotics among the most widely used systemic drugs in dermatology.¹ Recent years have brought to market numerous second-generation antihistamines intended to provide longer-lasting symptomatic relief and fewer side effects compared to predecessors. A new but less well-known addition to the field may offer further benefits and could prove useful in the dermatology clinic.

The Gold Standard
Diphenhydramine remains the gold standard of oral antihistamines. Marketed over-the-counter, it has been approved in the US for more than 60 years, is inexpensive, widely available, and generally effective. Diphenhydramine’s well-known
**For non-drowsy control of pruritus, a relative newcomer may provide benefits over older antihistamine agents.**

By Leon Kircik, MD

Sedating effects have been viewed as a benefit in certain circumstances. In fact, while recent studies shed doubt on the role of mast cell release of histamines in the pruritus of atopic dermatitis, many physicians continue to prescribe diphenhydramine to encourage sleep in patients kept awake by itch.

However, sedating effects of antihistamines can be problematic. For example, in patients with allergic rhinitis, sedating antihistamines are widely considered to exacerbate decreases in decision-making, verbal learning, and psychomotor skills associated with the condition, and sedating antihistamines have been documented to impair driving performance. Second-generation antihistamines do not readily pass the blood/brain barrier. Numerous studies have consistently demonstrated a decrease in sedating effects associated with second-generation antihistamines.

Interestingly, one comparison study found that all investigated antihistamines impaired driving to some degree when administered above their approved doses. Their “non-sedating” qualities have been a key marketing point for second-generation antihistamines as has once-daily dosing, a convenience versus administration of diphenhydramine every six hours.

**A Newcomer**

There are now several second-generation antihistamines available on the market; the newest has been approved in the US for just over a year. Levocetirizine (Xyzal, UCB/Sanofi-Aventis) is indicated for the relief of symptoms of perennial and seasonal allergic rhinitis and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children age six and older. It is supplied as a 5mg immediate-release tablet; Xyzal 0.5 mg/mL immediate-release oral solution received FDA approval in January. The immediate release tablet may be administered without regard to food. There are no concerns associated with impaired absorption related to fruit juices. Dosage for patients six to 11 years of age is 2.5mg each evening. Adults and patients 12 and older receive 5mg each evening. Some patients over age 12 may be adequately controlled on 2.5mg daily.

While some physicians may not be immediately familiar with levocetirizine, many have been administering a form of the drug for many years. Levocetirizine in a racemate of cetirizine (Zyrtec, McNeil Consumer Health), which also consists of equal amounts of dextrocetirizine. Interestingly, investigation of histamine-induced nasal response of cetirizine, levocetirizine, and dextrocetirizine found similar antihistamine activity for the former two but none for the latter.

When researchers compared the effects of cetirizine 5mg to that of levocetirizine 2.5mg or dextrocetirizine 2.5mg on histamine-induced wheal and flare response in healthy volunteers, they established that levocetirizine 2.5mg has comparable antihistamine activity to cetirizine 5mg, while dextrocetirizine conferred no pharmacodynamic effect.

Another investigation showed that levocetirizine provided greater inhibition of the wheal and flare response compared to four other antihistamines and placebo. Levocetirizine was deemed “most potent and consistently effective drug for inhibiting the histamine-induced wheal-and-flare surface areas.” The next most effective agents, ebastine, fexofenadine, and mizolastine, conferred effects similar to each other, while loratadine was the least potent drug. While levocetirizine, fexofenadine, and mizolastine inhibited the wheal-and-flare response after one hour (peak for inhibition after four hours), ebastine and loratadine outperformed placebo only after four hours.

Levocetirizine demonstrated significantly greater wheal inhibition over 24 hours in head-to-head comparisons with desloratadine in both healthy and allergic volunteers.

Another method of quantifying antihistamine effects is facial thermography. Upon histamine challenge, nasal skin increases in temperature; administration of antihistamines is expected to decrease nasal temperature toward baseline. Compared to fexofenadine, levocetirizine demonstrated similar antihistamine effects at two hours with more sustained activity at 24 hours among 30 randomized individuals subject to nasal histamine challenge. Nasal symptom reports and skin wheal and flare tests were also conducted on study participants and yielded similar results.
Dermatologic Uses

Evidence of levocetirizine’s efficacy in reducing the wheal and flare response suggests the drug may be a suitable option for management of chronic idiopathic urticaria, an approved use. Antipruritic effects of levocetirizine in chronic idiopathic urticaria are dose dependant, with daily administration of 2.5mg nearly twice as effective as placebo in reducing pruritus scores by week four. The 5mg daily dose—the approved dose—was slightly more effective, while 10mg daily yielded scores about two-thirds of those for placebo.1

Among 166 adult CIU patients randomized to receive levocetirizine 5mg daily or placebo over four weeks, levocetirizine was superior to placebo and demonstrated considerable efficacy (difference=0.78, P<0.001) that was maintained through four weeks.16 At one week and over the entire remaining study period, treated patients had fewer and smaller wheals. Importantly, treated patients had a 7.3-unit improvement in quality of life scores compared to 2.4 units in the placebo group. Treated patients also had higher productivity at work, losing just 0.3 days per patient per month, compared to 3.0 workdays lost per patient per month in the placebo group.

In another trial involving 100 evaluable CIU patients, levocetirizine 5mg daily again produced lower pruritus scores and fewer and smaller wheals over the treatment period compared to placebo.17 Based on a five-item health-related quality of life questionnaire, treatment produced about a 71 percent improvement in QoL score.

An analysis of data from two published trials along with a French national database (sample of 294 patients total) found that levocetirizine-treated patients experienced an additional mean 6.5 pruritus-free days per month (p < 0.001).18 Reduction in other medical costs (i.e. reduced cost of additional medications, medical procedures and hospitalizations) totally offset the incremental cost of treatment with levocetirizine; in fact, treatment with levocetirizine saved money for society, with a net gain of Euro 91.93 per patient per month.

But what about pruritus associated with AD? While the use of antihistamines to treat atopic dermatitis is widespread, little evidence clearly supports their use.1 AD-related pruritus has been associated with increased tissue histamine levels.1

In addition to its antihistamine activity, some evidence suggests that levocetirizine may confer anti-inflammatory effects that theoretically could prove useful in AD management. A cytokine antibody array found that levocetirizine (1 microM) enhanced the release of tissue inhibitor of metalloproteinases 1 and 4, matrix metalloproteinase 9, and heparin-binding epidermal growth factor.19 Furthermore, it was shown to attenuate the production of interleukin-1 beta and IL-7.

Data come from in vivo trials of levocetirizine in seasonal allergic rhinitis (SAR), which is characterized by an IgE-dependent inflammation that is linked to subsequent nasal obstruction. Thirty SAR patients were randomized to treatment with levocetirizine, desloratadine, or placebo for two weeks.20 Researchers evaluated total symptom score (TSS, including rhinorrhea, nasal itching, sneezing, and nasal obstruction) before and after treatment. Rhinomanometry, nasal lavage, and nasal scraping were used in all subjects before and after treatment in order to count inflammatory cells (conventional staining) as well as measure IL-4 and IL-8 (immunoassay).

While levocetirizine provided significant symptom relief and improved nasal airflow, desloratadine relieved symptoms but did not affect nasal airflow. Levocetirizine significantly reduced eosinophils, neutrophils, IL-4, and IL-8. Desloratadine diminished IL-4 only.

In their trial of levocetirizine and desloratadine for allergy-induced wheal suppression in allergic patients, Frossard

While the use of antihistamines to treat atopic dermatitis is widespread, little evidence clearly supports their use.1 AD-related pruritus has been associated with increased tissue histamine levels.
et al found that the activity of each agent against allergen-induced wheals “clearly shows the potential anti-inflammatory properties.” The team also investigated plasma levels, finding the mean total plasma concentration at 12 hours and 24 hours was higher for levocetirizine (58.1 +/- 13.4 and 20.0 +/- 8.1ng ml(-1), respectively) compared with desloratadine (0.82 +/- 0.24 and 0.45 +/- 0.16ng ml(-1)). Levocetirizine had higher mean unbound skin concentrations for 24 hours after intake (1.80ng g(-1)) than did desloratadine (0.07ng g(-1)). Receptor occupancy was greater for levocetirizine (54%) than for desloratadine (34%) at 24 hours.

FDA-submitted investigational trials along with various other studies document the efficacy of levocetirizine (versus placebo and other marketed antihistamines) for management of seasonal allergic rhinitis and perennial allergic rhinitis, which extends beyond the focus of this article.

Worth Considering

Unlike cetirizine, levocetirizine is considered a non-sedating antihistamine. In healthy volunteers, levocetirizine 5mg daily had no effect on memory, attention, and tracking performance at days one and four. Some patients in clinical trials reported somnolence, fatigue, and asthenia. In vivo investigations demonstrated significantly less impairment of driving ability as indicated by standard deviation of lateral position among patients treated with levocetirizine compared to diphenhydramine.

Levocetirizine offers a favorable safety profile. In addition to high affinity for the H1 receptor, levocetirizine has high bioavailability, rapid onset of action, limited distribution, and minimal hepatic metabolism. The drug is contraindicated in adults with end-stage renal disease and in children with impaired renal function.

Given its rapid onset of action, documented efficacy, and favorable safety profile, levocetirizine may be the agent of first choice for dermatology patients who are candidates for antihistamine therapy. Further investigation may elucidate anti-inflammatory actions of the drug and provide additional support for wider use in pruritic conditions, such as AD.

References

7. Xygal Prescribing information.