What are some guiding principles to the assessment of itch in the dermatology patient?

The symptom of itching complicates many dermatoses, often presents as a primary complaint that may mask an underlying systemic disorder, or might be its own isolated disease without other etiologies. In addition, many practitioners often use steroids as anti-itch therapy when they truly are not the most effective therapies against itch. To that end, the dermatologist needs to assess the pathophysiology and mechanisms that contribute to pruritus as well as understand and apply the appropriate therapeutic agents to alleviate the symptoms as well as arrest the itch-scratch cycle.

The important concept of mechanisms behind itching is that there is no single receptor for itching, analogous to pressure and temperature with individual corpuscles. The messages to the CNS for itch and pain are carried on C and Delta fibers, and the two stimuli often compete and inhibit the sensation of the other. For this reason, it is important for the patient to clearly interpret which is the predominant symptom to not only develop a differential diagnosis but also direct therapy. This has been seen with cholestatic pruritus and opioid-induced pruritus, which may explain the alleviation of itching with naloxone. There also exists the concept of overlap where interpretation of pain, itch, and burning are all intertwined, despite the lack of clinical inflammation or clear etiology.

What are the most frequently prescribed interventions for itch and why do they fail?

Itching to the dermatologist is similar to chest pain to the cardiologist, dizziness to the neurologist, or abdominal pain to the gastroenterologist, although maybe not to the same degree of morbidity. The symptom of pruritus is often the primary presentation, a complication of an underlying dermatosis or systemic disorder, or even a consequence of a therapy for another medical condition. Whatever the source, pruritus is usually a multifactorial problem involving neurological (neuropathic itch), chemical (neurogenic itch), physical (pruritoceptive itch), and even psychological (psychogenic itch) contributions. It is important for the dermatologist to remember that therapies to remedy itch must counter these mechanisms to be successful.

For control of itch more often than not patients are given steroids, which not only can mask an underlying cause but in reality serve as temporary solutions. Itching can cause insomnia, secondary infections, and can represent compulsions that the patient often doesn’t stop even when “busted” by the dermatologist in the office. The more important component is understanding how to interrupt the itch-scratch cycle with adjunctive therapies that can be used safely as maintenance.

What do we know about the benefits and risks of antihistamines?

Dermatologists use antihistamines differently than other specialists, often incorporating them as symptom relief than as maintenance. In these days of managed care and restricted formularies, it is difficult to get patients on agents that are often substituted for older molecules in generic or OTC preparations. The impact on patients might be manifest in a lack of...
First-generation antihistamines are capable of crossing the blood-brain barrier. In the brain, antihistamines block histamine (H1)-receptors. First-generation antihistamines have a wide pharmacologic profile: they easily cross the blood-brain barrier and non-selectively bind to and occupy 50-80 percent of the H1-receptors and cause central nervous system (CNS) depressant effects, such as drowsiness, sedation, and impaired psychomotor performance. Poor H1 selectivity can lead to anticholinergic effects that can include confusion, dry mouth, and urine retention.

Another characteristic of first-generation antihistamines is that they are short-acting with a dosing frequency of every four to six hours. This is often a paradox when patients need sustained relief throughout the night and might wake up itching or during the day when there is a need to balance control of itch and the ability to stay awake.

Second-generation antihistamines are commonly used as maintenance for chronic conditions, such as allergic rhinitis and urticaria. These antihistamines have less sedative effects and can be more selective for the H1-receptors with minimal or no antiserotonin, anticholinergic, or alpha-adrenergic blocking activity.

The newest addition to the family of antihistamines is levocetirizine (Xyzal, UCB Pharmaceuticals), which is FDA approved for chronic idiopathic urticaria. It is an enantiomer of the original cetirizine (Zyrtec) molecule but has demonstrated superior binding of H1 receptors and less activity across the blood-brain barrier. The concept of receptor occupancy is where dermatologists may see the benefits of this drug compared to previous molecules as it has been shown to have better binding. A study by Gillard et al evaluated the efficacy of levocetirizine 5mg in suppressing histamine-induced wheal and flare in humans at two different time points (four hours and 24 hours). The main objective of this study was to determine whether a parameter such as receptor occupancy could better explain and eventually predict the pharmacodynamic data and thereby the antihistamine potency. Receptor occupancy was calculated using the free concentrations present in the plasma at four and 24 hours after a single dose of each drug, which are the times allowing the receptor-ligand binding to reach equilibrium. At four hours, the RO for levocetirizine 5mg was 90 percent resulting in 100 percent wheal inhibition. At 24 hours, the RO for levocetirizine 5mg was 57 percent resulting in 60 percent wheal inhibition. The authors concluded that estimating in vivo RO, which takes into account both the affinity of the drug for the receptor and its free plasma concentration, is a far better predictor for human pharmacodynamics and hence antihistamine potency than considering in vitro affinity and plasma half-life only. The clinical relevance of these findings is unknown.

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Safety data are presented for the intention to treat (ITT) population. The ITT were all patients who made the definition of inclusion criteria (older than age 18 years, symptoms of rhinitis present during pollen season and on house dust exposure, positive skin test or specific serum IgE for at least house dust mite, and one pollen allergen) and took at least one dose of levocetirizine 5mg or placebo. Levocetirizine appeared to be well tolerated in adult patients (over age 18 years), particularly considering the length of the treatment. In the placebo group, 193 (70.7 percent) patients compared with 192 (69.1 percent) in the levocetirizine group reported at least one adverse event at some point during the six-month study. The most common adverse events were headache (23.2 percent placebo vs 24.5 percent levocetirizine), pharyngitis (20.5 percent and 19.8 percent, respectively), influenza-like symptoms (13.9 percent vs 14.0 percent), fatigue (7.0 percent vs 8.6 percent), somnolence (1.8 percent vs 6.8 percent), and gastroenteritis (5.1 percent vs 2.9 percent).

Q: Are there dangers or contraindications associated with these agents?

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Patients kept a daily diary of pruritus symptoms using a visual analog scale and were examined by a dermatologist at baseline and at each study visit. While the 25mg and 50mg doses showed little or partial improvement, the 75mg dose of sertraline achieved the greatest improvement in symptoms, and the 100mg dose added further benefit.

Sertraline significantly improved patient-reported itch scores by 30 percent compared to the worsening of scores by 24 percent in patients taking placebo. Scratching lesions found on 17 of the 21 patients at baseline improved in all patients after treatment. Excoriations also showed statistically better improvement with sertraline during the double-blind phase of the study. The number of itchy areas decreased significantly during the open label phase compared to baseline, and during the double blind phase with sertraline compared to placebo. Although few patients in the study had clinical depression at entry, “successful treatment of depression was not required for treatment of pruritus,” Dr. Mayo said.12

Dr. Bhatia is a consultant for UCB Pharma; He did not receive any honoraria or assistance for this article.

1. Wallengren, J Dermatologic Therapy, “Neuroanatomy and neurophysiology of itch,” pg 292-294
2. Bernhard, J Dermatologic Therapy, “Itch and Pruritus: what are they and how should itching be classified?" pg 289
12. Presentation title: Effects of Sertraline on Pruritus in Cholestatic Liver Disease: A Randomized Double Blind Placebo Controlled Crossover Study. Abstract 34

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