Intervene Early in Chronic Itch to Stop 'Rewiring'

BY BETSY BATES
Los Angeles Bureau

SANTA BARBARA, CALIF. — The "itch-scratch" cycle is the dermatologic equivalent of chronic pain syndrome, and should be treated as such, Timothy G. Berger, M.D., said at the annual meeting of the California Society of Dermatology and Dermatologic Surgery.

Just as with chronic pain, there is a "reduced threshold" phenomenon that occurs with chronic itch, he explained.

Chronicity not only lowers the threshold for the sensation of itch, it also increases the intensity of itch. Also like pain, short bursts of spontaneous itch may occur, even when the skin is clear.

"This has to do with anatomic rewiring in the central nervous system," said Dr. Berger, professor of clinical dermatology at the University of California, San Francisco.

"The premise for pain is to intervene early to stop that central rewiring. In itch, the same premise should be applied."

Dr. Berger explained that exciting advances in neurobiology have begun to elucidate the mechanisms of itch, although certain important pieces of the puzzle have yet to be found.

Importantly, researchers have discovered that itch is not, as previously believed, a minor sensation of pain.

Rather, "there are specific itch nerves and there are specific pain nerves," he said.

Itch-specific neurons are small, unmyelinated C fibers distributed into and near the epidermis, constituting about 10% of the sensory nerves. They have no response to pain, but do respond to histamine and certain plant species.

"These itch nerves have very extensive branches," with a single itch-specific neuron feeding an 8.5-cm area. That's why, "when there's something that hurts, there's a little spot that hurts. When you itch, your whole arm itches," he noted.

Specific receptors have been identified for pressure and for pain, but no specific itch receptor has been found, although Dr. Berger has confidence that one will be located. "It just can't be that there isn't one."

Dr. Berger said there are connections between pain and itch, although the two act independently. "Itch" and "pain" channels interact, and the neural elements mediating them are identical, though separate.

Itch can be blocked by pain, which is why scratching relieves itching.

Conversely, blocking pain neurons can heighten the sensation of itch, as in the case of opiates inducing pruritus.

Another intriguing aspect to itch is the role played by inflammatory mediators—neuropeptides. Even when a patient's itch does not have a primary inflammatory etiology, inflammation can develop in response to itch through neuropeptides.

This explains why drugs with anti-inflammatory properties can sometimes be effective in treating itch.

Dr. Berger reviewed several novel drugs for treating itch:

▶ **Thalidomide.** Especially effective in prurigo nodularis, this drug can be used for itch at dosages of 50-200 mg daily. It may increase the risk of neuropathy, and should be used cautiously in dosages higher than 100 mg/day, at which there may be an increased risk of thrombosis.

▶ **Mirtazapine (Remeron).** At a dosage of 15-45 mg nightly, this unique antidepressant has potent antihistamine properties. "It will occasionally work in patients when other medications have not worked," Dr. Berger said. It is sedating, but otherwise well tolerated.

▶ **Ondansetron (Zofran).** This serotonin 5-hydroxytryptamine-3 receptor blocker can be used in doses of 4 or 8 mg/day, especially for opiate-related itch.

▶ **Paroxetine (Paxil).** Another antidepressant, this is an SSRI unrelated to the others in its class. It is used for pruritus at a dosage of 20 mg/day. Its anti-itch properties are powerful enough that normal patients may develop pruritus upon stopping the drug.

Dr. Berger reported no conflicts of interest regarding any of these drugs. ■

For the Treatment of Chronic Pruritus, Old Drugs Are Making a Comeback

BY PATRICE WENDLING
Chicago Bureau

PARIS — Cannabinoid agonists and opioid receptor antagonists are among the novel treatments being explored for chronic pruritus, Dr. med. Sonja Ständer reported at the Fourth International Academy of Cosmetic Dermatology World Congress.

Cannabinoid receptors are promising therapeutic targets because they play an important role in a variety of processes, including metabolic regulation, pain, craving, and anxiety. They can be influenced directly by agonists or antagonists, or indirectly through manipulation of the endocannabinoid metabolism.

Two cannabinoid receptors, CB1 and CB2, are the primary targets of endogenous cannabinoids, and are expressed in central and peripheral neurons.

Recent research by Dr. Ständer and colleagues at the University Hospital in Münster, Germany, has shown that CB1 and CB2 are also present in abundance in human cutaneous nerve fibers and mast cells (J. Dermatol. Sci. 2005;38:177-88).

"Since cannabinoid receptors are expressed on cutaneous nerve fibers, topical cannabinoid agonists directly inhibit the transmission of pruritus and therefore represent a promising new therapeutic modality," she said.

In a pilot study, 22 patients with chronic pruritus, aged 25-82 years, were treated with one application of a topical cream containing a cannabinoid receptor agonist. Itching was significantly reduced in 14 of 22 patients, 8 patients were completely healed, and 8 were nonresponders.

Overall the response was very rapid, with patients experiencing relief within 2 days to 2 weeks, she said. The treatment was effective even in patients with a long history of itching.

Opioid receptor antagonists, developed to treat patients with opioid and alcohol dependence, represent another potential treatment. They block opioid receptors in the brain and spinal cord and activate pain-transmitting nerves, which themselves inhibit itch-transmitting neurons.

In a study of 133 patients with pruritic dermatoses and systemic diseases, naltrexone was evaluated at 25 mg in 6 patients (4.5%), at 50 mg in 61 (45.9%), at 75 mg in 4 (3%), at 100 mg in 57 (42.9%), and at 150 mg in 5 patients (3.8%). Therapy was maintained individually between 3 weeks and 6 years.

Response was very rapid, with patients experiencing relief within 2 days to 2 weeks.

DR. STÄNDER

A significant reduction in itching, defined as a 40%-60% decrease, or complete relief was reported within 11 days in 86 of 133 (64.7%) patients, although 46 (34.6%) did not respond. Among patients with chronic pruritus of unknown origin, 15 of 19 (79%) responded to the therapy.

With the exception of 28 patients, itching usually recurred when the therapy was interrupted, she said.

Dr. Ständer stressed that patients should be informed before treatment with naltrexone of potential side effects, such as nausea and vomiting. Such side effects are common, but are limited to the first few days of treatment.

Finally, single case reports suggest that selective serotonin reuptake inhibitors (SSRIs) also may relieve chronic itching.

An ongoing study of 80 patients with chronic pruritus has shown that itching can be relieved after 4 days of treatment with either paroxetine (Paxil) or fluvoxamine (Luvox) applied in low therapeutic dosages.

This approach isn't recommended for elderly patients because of cardiovascular side effects, such as arrhythmias and increased bleeding, associated with SSRIs, she said. ■

Pruritus Treatment Will Differ With Liver and Kidney Disease

SANTA BARBARA, CALIF. — Solutions exist for patients with severe pruritus associated with liver or kidney disease, but they may not be the same as for patients with nonmetabolic causes of itch, according to Timothy G. Berger, M.D.

In the case of liver disease, one must go to the source: the brain, Dr. Berger said at the annual meeting of the California Society of Dermatology and Dermatologic Surgery.

"The thing that you were taught in medical school about an increase in bile acids in the skin [of patients with liver disease] and all that? That's all wrong," said Dr. Berger, professor of clinical dermatology at the University of California, San Francisco.

Researchers at the National Institutes of Health conducted a number of "wonderful studies" that proved patients with liver disease do not properly metabolize endogenous opiates, and that "itching may be a complication of that problem," he said.

"Pruritus in liver disease originates in the brain by increased neurotransmission mediated by endogenous opiates," he explained. These patients, in fact, can get opiate withdrawal symptoms even though they are not taking opiates.

The solution, then, is to block opiates in the brain.

If topical steroids, phototherapy, and other standard pruritus therapies fail to work, start patients with liver disease on very low dosages of naltrexone (50 mg/day) and titrate upward. During the first week, prescribe 100 mcg of clonidine to avoid opiate withdrawal syndrome, he advised.

Dr. Berger cautioned colleagues to be sure patients are not actually taking opiates during initiation of therapy. He described the case of a 102-year-old patient with liver disease and severe itching who failed to inform him of the fentanyl patches she wore for her osteoporotic pain. "She had opiate withdrawal syndrome and had to be hospitalized for 2 days," he said. "So be careful."

Other approaches used for liver disease–related pruritus include cholestyramine or its better-tolerated alternative, colestipol; rifampin; albumin dialysis; and, as a last resort, liver transplantation.

Severe pruritus in patients with renal disease is less well understood.

"As opposed to liver disease and itch, here we have significant disease and we have no clue what the cause is," said Dr. Berger.

Treating xerosis, which may be profound in renal disease patients, and enhancing their dialysis regimen are good first steps.

Next, administer broadband—not narrow-band—UVB, which is more effective in renal disease–related pruritus.

Finally, prescribing a single, 200- to 300-mg dose of gabapentin (Neurontin) after each dialysis session has been shown to have dramatic effects.

"One pill and bam! The itching drops right off," he said.

—Betsy Bates

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