Efficacy of Gabapentin in the Management of Pruritus of Unknown Origin

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Generalized pruritus is a distressing symptom that can occur in several dermatologic and systemic disorders.1 Generalized pruritus of unknown origin is that which affects patients without any underlying dermatologic or systemic disorder and is unassociated with rash. It most commonly occurs in older patients and persists for long periods, from months to years. In many cases, the itching may be due to reduced water content of the skin, without overt dryness. Failure of the normal processing of the itching sensation along the course of central and peripheral sensory pathways may also play a role.2

REPORT OF CASES

CASE 1

An 80-year-old man was initially seen with generalized itching of longer than 12 months’ duration. It was intermittent but affected him daily. There was no associated rash, and the itching had increased in severity during a few months. He had undergone treatment with emollients, topical corticosteroids, and oral antihistamines, without much benefit. His medical history included ischemic heart disease, asbestosis, and peripheral vascular disease, for which he was taking simvastatin, furosemide, and clopidogrel hydrochloride. Treatment had been stopped for at least 3 months to ascertain whether this would relieve the itching, without any change. There was no personal or family history of atopy. Physical examination revealed no abnormality in the skin.

He was examined using routine hematologic (complete blood cell count) and biochemical tests (liver function tests and serum urea nitrogen and electrolyte profiles), the results of which were all normal. His serum creatinine level was marginally elevated at 1.8 mg/dL (162 µmol/L) (reference range, 0.6-1.5 mg/dL [50-130 µmol/L]). Chest x-ray films showed pleural plaques in both hemithoraces that were suggestive of asbestosis; they were confirmed by computed tomography of the chest and by a restrictive pattern on spirometry. Results of iron studies revealed a low serum iron level at 36 µg/dL (6.5 µmol/L) (reference range, 73-179 µg/dL [13-32 µmol/L]), although the transferrin level and total iron-binding capacity were normal. His total IgE level was elevated at 3019 IU/L (reference range, <100 IU/L).

Treatment was started with 1% menthol in aqueous cream and supplemental oral ferrous fumarate to increase the iron level. Although the iron level normalized within 8 weeks, there was no improvement in the itching. Sedative antihistamine therapy (50 mg of hydroxyzine hydrochloride at bedtime) and non-sedative antihistamine therapy (180 mg of fexofenadine hydrochloride once daily) also conferred no benefit. A course of broadband UV-B treatment was started, but the patient could not tolerate it because of increased itching within 2 hours of each phototherapy session. An empirical course of prednisolone (30 mg/d), tapered and stopped within 3 weeks, also had no effect on the pruritus.

CASE 2

A 72-year-old man had a 2-year history of generalized itching unassociated with rash. It routinely prevented him from sleeping through the night. He had tried different emollient creams without improvement. His medical history included asthma, interstitial pulmonary fibrosis, and hiatus hernia, for which he was taking aminophylline and using inhaler devices. On physical examination, no rash was evident. His complete blood cell count was normal, except for an eosinophil count of 2400/µL (reference range, 0-400/µL). Results of liver function tests, serum urea nitrogen and electrolyte profiles, iron studies, and autoantibody screens were normal. The IgE level was elevated at 169 IU/L (reference range, <100 IU/L). Chest x-ray films showed bilateral basal fibrosis, and spirometry demonstrated a restrictive pattern, suggestive of interstitial fibrosis.

Treatment with oral antihistamines (25 mg of hydroxyzine hydrochloride at bedtime) and 1% menthol in aqueous cream was not effective in relieving itching. Treatment with topical corticosteroids, emollients, and oral cetirizine hydrochloride (10 mg once daily) also did not improve his symptoms. Broadband UV-B therapy 3 times a week for 6 weeks, a reducing course of oral prednisolone for 8 weeks, oral dothiepin hydrochloride for 10 weeks, and 2 mg of ketotifen fumarate twice daily for 4 months also had no effect.
Treatment of generalized pruritus of unknown origin can be challenging, and topical and systemic agents have been used successfully. Topical agents include coolants (menthol), antihistamines (a eutectic mixture of local anesthetics), antihistamines (doxepin hydrochloride), corticosteroids, and substance P depletors (capsaicin). Most patients, however, will require systemic agents such as antihistamines (histamine1 and histamine2 receptor antagonists), dothiepin, paroxetine hydrochloride, prednisolone, opioid antagonists (naltrexone hydrochloride), and antiserotoninergic medication. There are anecdotal reports of the usefulness of anesthetic agents such as propofol and lidocaine hydrochloride. Our patients did not respond to topical or oral medications that are normally used in treating generalized pruritus of unknown origin.

Recently, gabapentin, an antiepileptic agent, has been reported to be an effective antipruritic agent in brachioradial pruritus. It has been suggested that gabapentin may be useful in chronic itching that is unresponsive to other treatments.

In our patients, we started gabapentin therapy at a dose of 300 mg/d on day 1, increasing it to 600 mg/d and 900 mg/d on days 2 and 3, respectively. Thereafter, the dosage was increased to 1800 mg/d during the next 3 to 4 weeks, titrating the dose to symptom control. Both patients had an excellent response, with complete control of the itching within the first month. They have continued with a maintenance dosage (based on symptom control) of gabapentin and have remained symptom free for longer than 9 months, with no adverse effects due to the medication.

Pruritus is a distinct sensation that evokes a desire to scratch. It is transmitted by C fibers that end in specialized receptors localized on the multimodal endings close to the dermoepidermal junction. These fibers synapse in a specific class of dorsal horn neurons and ascend up the spinal cord in the lateral spinothalamic tract. Supraspinal processing of the itching sensation is attributed to activation of the anterior cingulate cortex, supplementary motor area, and inferior parietal lobe in the brain, with a left hemisphere predominance. Different pharmacological mediators of the itching sensation have been proposed, including histamine phosphate, prostaglandin E1, serotonin (5-HT), substance P, opioid peptides, calcitonin gene–related peptide, IL-2, and tryptase. Specific inhibitors of these mediators have been shown to alleviate itching to varying degrees. A recent study demonstrated the efficacy of paroxetine (a selective serotonin reuptake inhibitor) in treating generalized pruritus by its binding to serotonin transporters on presynaptic nerve endings. This prevents neural reuptake of serotonin, which initially increases the amount of serotonin in the synapse. With prolonged reuptake inhibition, the postsynaptic 5-HT receptors are downgraded, and serotonin release is decreased. Opioid receptors also play a part in pruritus by means of peripheral and central mechanisms. Administration of morphine sulfate, an opioid agonist, causes intense pruritus in most patients. Opioid receptor antagonists in experimental mice have been shown to be effective in preventing scratching in response to itching.

Gabapentin is an antiepileptic drug that has been used in different conditions associated with chronic pain and, recently, in pruritic disorders. It has a novel molecular structure, and although its precise mechanism of action is unknown, various hypotheses have been proposed to explain it. Its primary effect is inhibition of voltage-dependent calcium ion channels located in the spinal cord (with particular high density in the superficial laminae of the dorsal horn), inhibiting the release of excitatory neurotransmitters. Gabapentin neither acts directly on the γ-aminobutyric acid receptor nor affects the reuptake of γ-aminobutyric acid. It increases the synthesis of γ-aminobutyric acid from glutamate by altering the activity of glutamic acid decarboxylase in neurological tissue. Its effect on pruritus may be central and peripheral. Gabapentin is known to secondarily inhibit calcitonin gene–related peptide (a mediator of itching) release from primary afferent neurons through a primary increase of γ-aminobutyric acid in the spinal cord. Furthermore, it has been hypothesized that opioid receptors are involved in the mechanism of action of gabapentin. Although not directly agonistic or antagonistic to the opioid receptors, modulation of the μ-opioid receptors may affect the central perception of itching. Opioid peptides also have a peripheral action, potentiating itching due to other agents.

Gabapentin is well absorbed orally and does not inhibit or induce hepatic enzyme function. Because of the pharmacokinetics of gabapentin, drug interactions are unlikely. The initial dosage of gabapentin is 300 mg/d and can be increased up to 1200 mg 3 times a day. It has a high toxicity ratio, minimizing the chance of adverse effects with even very high overdoses. Gabapentin treatment should not be discontinued abruptly but rather tapered gradually, as discontinuation can lead to withdrawal-related adverse effects. The most common adverse effect is sedation. Rarely, it can cause pancytopenia, cholestasis, hypersensitivity syndrome, and dyskinesia. We recommend gabapentin treatment for patients with generalized pruritus of unknown origin that is unresponsive to the usual treatment modalities.

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