Erythromelalgia: response to serotonin reuptake inhibitors.

By Rudikoff D, Jaffe IA


Erythromelalgia is a painful disorder of the extremities characterized by redness, swelling, a burning sensation, and an increase in skin temperature exacerbated by exposure to heat. An early description was reported by Mitchell in 1878. He coined the term erythromelalgia to denote the clinical features of redness (erythros), involvement of the extremities (melos), and the symptom of pain (algos). Later authors suggested the name "erythermalgia" to emphasize elevated temperature of the affected extremities, and others have used the term "erythralgia". There have been two recent comprehensive reviews of erythromelalgia.

The pathophysiology of erythromelalgia is poorly understood but there is evidence that serotonin (5-HT) may be involved in at least some cases. The warm congested extremities suggest that vasodilation may be involved in its pathogenesis. 5-HT is a biogenic amine that influences vascular endothelium and platelet function. The serotonin antagonists, methysergide and pizotifen have been reported to be effective in some cases of juvenile-onset erythromelalgia, further supporting a 5-HT mechanism.

It is believed that serotonin reuptake inhibitors are effective in the treatment of depression because of their ability to inhibit the reuptake of 5-HT in certain neuronal cells. One of us (I.J.) recently reported the successful treatment of Raynaud's phenomenon with serotonin reuptake inhibitors. Although erythromelalgia has been called the "antithesis of Raynaud's", there are cases of the coexistence of the two in the same patient. It seemed reasonable, therefore, that serotonin reuptake inhibitors might be useful in the treatment of erythromelalgia.

**CASE REPORTS**

Case 1

A 63-year old woman noted the abrupt onset of marked painful erythema of both feet that was so intense that it necessitated immersion of her feet in ice water. Her attacks were less frequent and less severe in the winter. Corticosteroids administered topically, intralesionally, and systemically, as well as buprofen, aspirin, nortriptyline, propranolol, and intravenous immunoglobulin were without benefit.

The feet showed marked plantar erythema, warmth, and tenderness. All routine blood studies including platelet count were within normal limits. Doppler studies, bone marrow studies, electromyography, tests of thyroid function, and all rheumatic serologies were negative. Administration of venlafaxine, 37.5 mg twice daily, resulted in a rapid relief of her symptoms. She has had no major attacks in 14 months.
Case 2
A 68-year old woman with chronic lymphocytic leukemia for 10 years had been treated with fludarabine. Six months previously, the patient suffered a right hip fracture that required internal fixation. Her postoperative course was complicated by staphylococcal sepsis and meningitis. Severe itching, burning pain, swelling, and marked redness of her feet and ankles occurred and was exacerbated by warmth and dependency. She was able to sleep only by use of a device that delivered ice cold water in plastic tubing wrapped around her feet. Her feet were bright red, warm, and edematous. Pedal pulses and neurologic examination were normal. Complete blood cell count, including platelets, and all blood chemistries were normal. A biopsy specimen from the dorsum of the right foot revealed scattered foci of hydropic change in the epidermis. A mild perivascular infiltrate of predominantly mononuclear cells surrounded vessels of the superficial plexus in the dermis. No intravascular thrombi were noted.

There was no improvement of her symptoms with low-dose aspirin, indomethacin, ciproheptadine, amitriptyline, doxepin, prednisone, or propranolol. A right-sided lumbar block failed to provide relief. The patient was given venlafaxine 37.5 mg twice daily. She noted marked improvement in her symptoms by the third day.

Case 3
A 52-year old woman had a 7-month history of swelling, redness, burning, and increased temperature of her hands and feet. Her symptoms were aggravated by warmth and relieved by ice. All treatments including aspirin had failed to relieve her discomfort. The hands and feet were blue-red, warm, and swollen. Routine hematologic studies including platelet count were normal. Scleroderma 70 and anticentromere antibodies were negative. A biopsy specimen of the dorsum of the right foot revealed minimal dermal fibrosis.

The patient was given fluoxetine 20 mg per day without benefit. She was then given sertraline 50 mg twice daily; marked improvement was noted after 3 days. Six months after successful treatment of her erythromelalgia she was found to have overt scleroderma.

DISCUSSION
All our patients experienced marked clinical improvement in their symptoms of erythromelalgia when given serotonin reuptake inhibitors. These patients were refractory to all other treatments. There has been no effective treatment for adult-onset idiopathic erythromelalgia. This is in contrast to erythromelalgia associated with thrombocytosis, which responds to aspirin, or erythromelalgia resulting from an underlying disease, which usually responds to treatment of the basic disorder.

5-HT is a vasoactive substance involved in central and peripheral neurotransmission.
and platelet function. It may cause vasoconstriction or vasodilation depending on the vessel involved and the integrity of the endothelium.\textsuperscript{10}

Two of our patients responded to venlafaxine, a serotonin reuptake inhibitor that also has an effect on the reuptake of norepinephrine.\textsuperscript{17} To determine whether norepinephrine reuptake was necessary for a clinical response, we treated our third patient with fluoxetine, which blocks only serotonin reuptake.\textsuperscript{13} She failed to respond and was then given sertraline, another serotonin reuptake inhibitor, that also blocks only serotonin reuptake. Because she responded, we conclude that blocking the reuptake of norepinephrine is not necessary for efficacy. We cannot explain why our third patient did not respond to fluoxetine but did respond to sertraline. A similar variability of response to serotonin reuptake inhibitors was seen in the treatment of Raynaud's syndrome.\textsuperscript{14}

REFERENCES

2. Mitchell SW. On a rare vaso-motor neurosis of the extremities, and on the maladies with which it may be confounded. Am J Med Sci 1878;76:2-36