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Lidocaine and Mexiletine Therapy for Erythromelalgia

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

A 25-YEAR-OLD white man presented with a life-long history of severe, sometimes excruciating pain in his legs, which were constantly red and hot. He insisted on having his legs and feet constantly in ice water to relieve his severe discomfort. He required treatment with oxycodone and acetaminophen (Percocet) every 4 hours for pain.

His mother recalled that from the age of 2 years his feet and legs intermittently turned a bright red, were hot to the touch, and were extremely tender. The redness and associated pain in his legs and feet became persistent. He learned to soak his feet in ice water for comfort as needed during classes in high school. He completely avoided wearing socks and only wore shoes when necessary. He attempted to play sports but had to stop intermittently to cool his feet with ice water because of severe burning pain and redness of both feet. When he was in high school, he took a job as a lifeguard during the summer, soaking his feet in the water. His social life was curtailed. He had a fan blowing on his feet all night, and he would get up for 1 to 2 hours during the night to soak his feet in ice water. He developed similar but milder pain in the hands.

There had never been a period in his life when the pain had resolved despite treatment with multiple medications, including tricyclic antidepressants, systemic corticosteroids, and nonsteroidal anti-inflammatory drugs; transcutaneous electrical nerve stimulation; and multiple pain medication regimens that were coordinated by pain clinics. He started drinking heavily at age 13 years. He used cocaine, diazepam, marijuana, oxycodone and acetaminophen, and alcohol to try to get rid of the pain. He thought that cocaine worked best for the pain. He underwent detoxification as an outpatient in 1994. There was no family history of similar problems, and he was otherwise in good general health.

During the 6 months before presentation, his pain worsened. He soaked his feet in cold or ice water to the point that he had them constantly submerged. He developed multiple small painful ulcers over his feet, ankles, and legs. A trial of sympathetic nerve blockade and epidural corticosteroids (exact procedure by history unclear) 3 months previously had given temporary (3-5 days) relief. Afterward, however, the pain worsened.

Examination revealed a patient in discomfort, with his feet in a large bucket of ice water, which he carried

with him. Grimacing and considerable expressions of pain were noted, and he had difficulty talking because of pain. Multiple superficial fibromembranous to purulent-appearing ulcers punched out over the lateral aspect of the feet, ankles, and the lower part of both legs. Markedly erythematous and hot legs and feet (**Figure 1**) were noted. Physical examination and history were consistent with the diagnosis of erythromelalgia.

Investigation revealed a small-fiber neuropathy affecting the upper and lower extremities. The affected areas were hot, with an increased laser Doppler flow, and a relatively low transcutaneous oxygen level was noted. The patient was hospitalized and a morphine patient-controlled analgesia pump was started for pain. Topical treatments included continuous antiseptic wet dress-



Figure 1. Patient at time of presentation (note red legs with associated ulcers).

ings changed every 3 hours and daily whirlpool bath. Naproxen treatment was added to the regimen. The amitriptyline hydrochloride dosage was increased to 150 mg orally each day. The redness and pain persisted.

THERAPEUTIC CHALLENGE

Erythromelalgia is frequently recalcitrant to treatment. Many therapeutic modalities have been reported to be helpful in individual cases. Our challenge was to find an effective treatment regimen for the extreme pain suffered by this patient.

SOLUTION

Treatment was started with intravenously administered lidocaine followed by orally administered mexiletine hydrochloride. An infusion of 450 mg of lidocaine was planned. After approximately 200 mg, a 90% improvement in pain was reported. Mexiletine hydrochloride was initiated the next day at 300 mg twice daily, and the dosage was then escalated to 300 mg 3 times a day. The pain continued to improve. The patient was weaned from morphine, and the morphine was stopped 3 days later and replaced by tramadol hydrochloride given orally. He was discharged after being hospitalized for 9 days. Follow-up revealed that his improvement was sustained for 2 years (**Figure 2**). He reports that his pain is 90% to 95% better. Although his feet and legs are still red most of the time, for the first time in his life they occasionally turn pink or even flesh-colored. He wears shoes and socks and works as a dispatcher. He sleeps without a fan.



Figure 2. Patient 2 years after treatment; ulcerations have resolved, postinflammatory hyperpigmentation is present, and legs are no longer erythematous.

COMMENT

Erythromelalgia is a rare clinical syndrome of usually symmetrical extremity pain characterized by redness and a marked increase in skin temperature. It was first described in 1878 by Mitchell,¹ who coined the term *erythromelalgia* to denote the features of redness (*erythros*), involvement of the extremities (*melos*), and pain (*algos*). Smith and Allen² suggested the term *erythermalgia* to emphasize the central diagnostic and clinical importance of elevated temperatures in the affected acral areas. The characteristic changes are usually intermittent, although they rarely may become constant. Characteristically, they are provoked by an increase in ambient temperature or by exercise. The lower extremities are more frequently involved than the upper extremities. Patients typically obtain relief by elevating and cooling the involved extremity. Relief is temporary, and in some patients immersion injury develops from prolonged exposure to cold water.³ Erythromelalgia has been divided into primary (idiopathic) and secondary (associated with other diseases) types. Secondary erythromelalgia is most commonly associated with myeloproliferative disorders, such as thrombocythemia or polycythemia rubra vera.^{4,5}

The pain associated with erythromelalgia is often severe and recalcitrant. In a recent study of quality of life in 99 patients with erythromelalgia who were seen at the Mayo Clinic,⁶ quality of life scores were depressed in all health domains compared with those of an age- and sex-matched control population. When reexamined, 3 patients had committed suicide, which was attributed to the pain caused by the erythromelalgia.

The pathogenesis of this syndrome is unclear. Whether this is a disorder of the vasculature or of nerves needs further study. Both vascular abnormalities (increased blood flow, increased temperature, paradoxically decreased PO₂ on transcutaneous monitor) and neuropathies (both small- and large-fiber neuropathies in a high proportion of patients) are typically observed (M.D.P.D., unpublished data, 1999).

Erythromelalgia can be extremely recalcitrant to treatment. Although treatment with aspirin was initially reported to be the miracle cure for this disorder, clinical experience has not demonstrated high success rates in the majority of patients with erythromelalgia seen at our medical center. Patients who are resistant to aspirin therapy try a multitude of therapeutic modalities to control their pain,⁶ often without success.

In the case described here, an intravenous infusion of lidocaine was successful in treating the neuropathic pain associated with erythromelalgia; then mexiletine therapy was given orally. There was a profound improvement in the level of pain and an improvement in the manifestations of the syndrome, which coincided with the initiation of these medications. The patient also was also treated with tramadol and amitriptyline but had been taking these medications for some time without an improvement in his symptoms.

Local anesthetics such as lidocaine and mexiletine prevent or relieve pain by interrupting nerve conduction. Mexiletine is an oral analog of intravenous lidocaine (both class IB antiarrhythmia drugs) that shares the

ability to block the sodium channel. Lidocaine and mexiletine have been used to treat neuropathic pain secondary to diabetic neuropathy, spinal cord injury, chronic pain syndromes secondary to peripheral nerve injury, fibromyalgia, and adiposis dolorosa (Dercum disease).⁷⁻¹³ In clinical practice, lidocaine therapy given intravenously has been used as a predictor for response to mexiletine therapy given orally.

When administered systemically, mexiletine and lidocaine (both class IB antiarrhythmia drugs) may exert their analgesic effects via peripheral, central, or mixed mechanisms.¹⁴ Evidence is emerging that lidocaine and mexiletine may exert their antinociceptive effect through a central mechanism. Electrophysiologic studies aimed at elucidating the site at which lidocaine and tocainide exert their antinociceptive action provide compelling evidence in support of a central site of action.¹⁴⁻¹⁶ With regard to a peripheral mechanism, animal models of nerve injury^{14,17-20} and a model of phantom limb pain in humans²¹ seem to indicate that after nerve injury peripheral mechanisms may develop that are responsive to the blockade of sodium channels.

Our patient had profound relief of his pain after the lidocaine infusion and sustained relief once a therapeutic level of mexiletine was attained.

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Submissions

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