Primary Erythromelalgia in a Child Responding to Intravenous Lidocaine and Oral Mexiletine Treatment

Aruna Nathan, MD; John B. Rose, MD; Jessica W. Guite, PhD; David Hehir, MD; and Karen Milovcich, CRNP

ABSTRACT. Erythromelalgia is a rare, chronic, debilitating condition characterized by redness, warmth, and severe burning pain of the distal extremities. The feet are more commonly affected than the hands. Pain is precipitated by increases in temperature and by exercise. Patients often obtain relief by immersing the affected extremity in cold water. All conventional pain management techniques had failed to relieve our patient’s symptoms, and he obtained some relief only by soaking his affected extremities in ice water. He had experienced minimal benefit from seeing a pain psychologist, who helped him develop techniques to cope with the pain. At the time of presentation, the patient’s episodes of pain had increased to 15 to 20 per day, and there was evidence of chronic immersion injury to the skin of his feet. Before his most recent hospitalization, the pain had spread to involve his hands as well. The patient was overwhelmed with anxiety and could not participate in school or social activities at the time of admission. During his current hospitalization, he did show some therapeutic response to sodium nitroprusside infusion, which unfortunately had to be discontinued because of side effects and because his family desired to leave the ICU environment, which was stressful to the patient. He also had some response to lumbar epidural infusion of local anesthetics, which could not be continued because he found the motor blockade that accompanied his analgesia intolerable. However, intravenous lidocaine infusion, with subsequent transition to oral mexiletine therapy, proved very effective in reducing the frequency and severity of the pain episodes. The patient was discharged from the hospital with oral mexiletine therapy and has been monitored at the pain management clinic. He returned to and completed school, attended summer camp, and enjoys an active happy life. He walks without precipitating pain in his feet and sleeps 9 to 10 hours every night. He has needed to soak his feet on only 4 occasions in the 6 months since his discharge from the hospital. His quality of life has improved significantly. He has shown no evidence of liver toxicity, and his mexiletine levels have been stable. 

Erythromelalgia is a rare, chronic, debilitating condition characterized by redness, warmth, and severe burning pain in the distal extremities. The feet are more commonly affected than the hands. Pain is precipitated by increases in temperature and by exercise. Patients often obtain relief by immersing the affected extremity in cold water. The pain is often refractory to treatment. For many patients, multiple pain medications have been useless in achieving complete relief of pain symptoms. Previous reports of erythromelalgia among adolescents indicated prolonged relief of pain with sodium nitroprusside infusions, epidural infusions of local anesthetics, or gabapentin treatment. We present a case of an 11-year-old, white, male child with primary erythromelalgia, whose initial symptoms started in his preschool years and whose childhood was marked by escalating episodes of pain with warmth and redness of his feet, precipitated especially by increases in temperature and by activity. All conventional pain management techniques had failed to relieve our patient’s symptoms, and he obtained some relief only by soaking his affected extremities in ice water. He had experienced minimal benefit from seeing a pain psychologist, who helped him develop techniques to cope with the pain. At the time of presentation, the patient’s episodes of pain had increased to 15 to 20 per day, and there was evidence of chronic immersion injury to the skin of his feet. Before his most recent hospitalization, the pain had spread to involve his hands as well. The patient was overwhelmed with anxiety and could not participate in school or social activities at the time of admission. During his current hospitalization, he did show some therapeutic response to sodium nitroprusside infusion, which unfortunately had to be discontinued because of side effects and because his family desired to leave the ICU environment, which was stressful to the patient. He also had some response to lumbar epidural infusion of local anesthetics, which could not be continued because he found the motor blockade that accompanied his analgesia intolerable. However, intravenous lidocaine infusion, with subsequent transition to oral mexiletine therapy, proved very effective in reducing the frequency and severity of the pain episodes. The patient was discharged from the hospital with oral mexiletine therapy and has been monitored at the pain management clinic. He returned to and completed school, attended summer camp, and enjoys an active happy life. He walks without precipitating pain in his feet and sleeps 9 to 10 hours every night. He has needed to soak his feet on only 4 occasions in the 6 months since his discharge from the hospital. His quality of life has improved significantly. He has shown no evidence of liver toxicity, and his mexiletine levels have been stable. 

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mg, twice daily), oxycodone (4 mg, every 4 hours), aspirin (325 mg, every day), morphine sulfate (2.5 mg, intravenously, every 3 hours), and nalbuphine (4 mg, intravenously, every 4 hours). The patient obtained some relief of his pain by soaking his feet in cold water for 15 minutes. The patient and his parents reported that his pain had been increasing in frequency and severity, with 15 to 20 excruciating pain episodes each day, accompanied by warmth and redness of his extremities. The frequency and duration of foot soaking had also increased, providing only minimal relief. The patient appeared to be overwhelmed with anxiety. He was unable to sleep >1 hour at night and had not been attending school. The pain had also extended to his hands and was unresponsive to any of his current medications. There was evidence of chronic ischemic injury to the skin on his feet. The skin covering his feet was thickened, reddened, and macerated but there were no ulcerations. The patient’s hands had not been involved until 1 month before hospitalization. The pain in his hands was less frequent and milder than that in his feet, and the patient rarely immersed his hands in ice water. His hands were warm and red, and the skin was only slightly thickened.

The patient’s history was significant for pain-related behavior first identified during his preschool years, when he was noted to have episodes during which he would cry, sit on the floor, take off his shoes and socks, hold his feet, and refuse to participate in activities with other children. The painful episodes increased with time, severely restricting activity. The pain, which was associated with redness and warmth of the feet, was made worse by heat and exercise and showed some improvement with soaking of the patient’s feet in cold water. There was no family history of erythromelalgia.

On evaluation, MRI scans of the patient’s spine, brain, and feet, a bone scan of his feet, nerve conduction studies, and lower-extremity electromyograms were all found to be normal. Blood tests, including a complete blood count, basic metabolic panel, liver function tests, C-reactive protein, antinuclear antibodies, vitamin B6 and B12, and folate level tests, and coagulation tests, all yielded results within normal limits. Fabry’s disease can present with similar symptoms. However, our patient’s white blood cell β-galactosidase (111.4 nmol/hour per mg protein) and α-galactosidase (70 nmol/hour per mg protein) levels were normal. He had been treated for calcaneal apophyseitis when he was 9 years of age, although MRI scans of his foot at that time revealed no abnormality. He had also undergone bilateral excisions of Morton’s neuromas. A spurious elevation of his platelet count was noticed at that time, the diagnosis of erythromelalgia was considered, and aspirin therapy was initiated 2 years before his current hospitalization. Aspirin therapy was discontinued because it proved ineffective. Quantitative sensory testing, capillaroscopy, and thermography were not performed because these studies are not available at our institution. The patient had participated previously in a brief course of treatment with a psychologist, to facilitate pain coping. However, the patient had not had any contact with a psychosocial support provider in the year before his current admission. Before this hospitalization, trials of ibuprofen, naproxen, tramadol, gaba- pentin, amitriptyline, and topical lidocaine patches had failed to relieve his pain.

After admission to the hospital, the patient began treatment with morphine, oxycodone, and nalbuphine for analgesia and pentoxifylline for improved blood flow. The pain management service, which included medical, nursing, and psychologic staff, was consulted. The patient was transferred to the ICU and treated with nitroprusside infusion (initial dose of 0.5 μg/kg per minute, which was increased in increments of 0.5 μg/kg per minute every 8-12 hours to a maximal dose of 5 μg/kg per minute). This was abandoned after 72 hours because the patient experienced periods of hypotension (pH 7.36; Pco2: 28 mm Hg; Po2: 117 mm Hg; HCO3 concentration: 15 mmol/L; base excess: −9; lactate concentration: 0.9 mmol/L). Although the patient experienced relief of his bilateral hand pain, nitroprusside treatment was not restarted because the patient experienced no analgesic benefit for his bilateral foot pain and the patient and his family desired to leave the ICU and discontinue the patient’s analgesic line. A lumbar epidural catheter was placed at the L4–L5 interspace, and an epidural infusion (0.125% bupivacaine with 5 μg/mL fentanyl) was initiated at 0.2 mL/kg per hour. The epidural bupivacaine infusion gave the patient almost complete analgesia and uninterrupted sleep. However, the bupivacaine concentration needed to be lowered because of irritation and pain of the lower extremities. Decreasing the bupivacaine concentration resulted in an increase in the frequency and severity of pain episodes. After 1 week of partial pain relief, the epidural catheter was removed. At that time, the patient began treatment with a transdermal clonidine patch (0.2 mg), to be changed every 7 days. The pediatric psychologist working with the pain management service maintained close contact with the patient and his family throughout this time, to provide support and consultation regarding nonpharmacologic pain coping strategies. Treatment with sertraline (25 mg, once daily) was initiated at this time through consultation with the psychiatry service, to address continued symptoms of anxiety and to facilitate engagement in developmentally appropriate activities and adaptive pain coping strategies. All other medications were discontinued. The patient’s pain stabilized at 4 to 6 episodes per day, with occasional foot soaks at night. To enhance physical functioning and participation in activities of daily living, the patient was transferred to the hospital’s rehabilitation unit for a graduated exercise program. During the patient’s admission to the rehabilitation unit, increasing activity was associated with severe episodes of pain, warmth, and redness of his feet. The frequency of pain episodes eventually increased to 19 or 20 episodes in a 24-hour period, with an increased need to soak the feet in ice water to obtain pain relief. To control these acute episodes, intravenous lidocaine infusion was considered, discussed with the family, and subsequently initiated. It is the policy in our institution for children receiving intravenous lidocaine infusions to be monitored in an ICU. Lidocaine toxicity can result in neurotoxicity, with central nervous system depres- sion or seizures, and cardiovascular toxicity, with hypotension, arrhythmias, and cardiovascular collapse. Therefore, the patient was transferred back to the PICU, and a lidocaine infusion was initiated at 16.5 μg/kg per minute and titrated in 20% increments to achieve a blood lidocaine level of 2 to 5 μg/mL. This was maintained until the patient’s pain episodes and soaking spells decreased to 1 to 3 per day and his sleep remained undisturbed for a total of 4 nights. His electrocardiographic status was continuously monitored during this time, without any adverse effects. The patient was then transitioned to orally administered mexiletine (75 mg, once daily). The dose was increased over a 3-week period to a maintenance dose of 150 mg, 3 times daily. The patient tolerated this dose escalation without difficulty, and all his pain episodes were relieved, although he was not pain free. Blood levels of mexiletine stabilized at 0.9 μg/mL, and the patient was discharged from the hospital after a hospital stay of 45 days. Mexiletine levels (range: 0.7-1.4 μg/mL) continue to be monitored at regularly scheduled outpatient appointments, through the pain management clinic. The frequency, duration, and intensity of the patient’s pain episodes have decreased significantly. The patient returned to school, without precipitating pain in his feet, and sleeps for 9 to 10 hours every night. He has rarely soaked his feet in ice water in the 6 months since his discharge from the hospital. When he does soak his feet, it is usually because he is.

**Fig 1.** The patient’s feet and hands at the time of admission to the hospital during an episode of severe bilateral foot pain.
concerned that pain may develop after vigorous activity. On 4 occasions, it was because he actually experienced pain (usually after walking for a long time). However, the patient claims that he has not experienced the severe burning pains he routinely experienced before starting mexiletine therapy. The lidocaine and mexiletine relieved the warmth and some of the redness of his feet, but the thickened, erythematous, and macerated skin took weeks to resolve after the mexiletine therapy began. The quality of life of the patient and his family has improved significantly.

DISCUSSION

Erythromelalgia is considered by some to be attributable to maldistribution of skin microvascular blood flow, with increased flow through arteriovenous shunts and inadequate nutritive flow.6 Mork et al7 also showed reduced skin capillary density during attacks of erythromelalgia. Prospective studies of a group of patients with erythromelalgia suggest a vasculopathy with increased shunting and flow and increased local cell metabolism or a small-fiber neuropathy.8 Littleford et al9 demonstrated an increased vasoconstrictor tendency among erythromelalgia patients and reduced sympathetically mediated vasomotor reflexes in both affected and unaffected areas. These areas of dysfunction appear to be widespread. Other studies indicated impairment in neurogenic control of skin perfusion in erythromelalgia.10 The tremendous variety of proposed pathophysiologic mechanisms responsible for erythromelalgia explains in part the large number of therapies that have been advocated and the variability in responses to these clinical treatments. Erythromelalgia has been classified into primary and secondary forms. Secondary erythromelalgia has been associated with myeloproliferative and hematologic diseases, disorders of the autonomic nervous system, drugs, viral infections, and pregnancy. In a review of data for 168 patients with erythromelalgia monitored at the Mayo Clinic, 4.2% of the patients had experienced symptoms since childhood.1 Symptoms were intermittent for 97% of the patients and constant for 3%. There was a significant decrease in survival rates, compared with those expected for persons of similar age and gender. In a survey of 99 patients in this group, 84 different types of medications had been used.1 Apart from the simpler analgesic modalities, a range of treatments, including tricyclic antidepressants, anticonvulsants, local anesthetics, clonidine, and opioids, have been tried for patients with erythromelalgia, with varied success. More recently, lidocaine patches, epidural local anesthetic infusions, sodium nitroprusside infusions, and gabapentin have been tried.2–4,11 The analgesic effects of sodium nitroprusside are thought to be primarily peripheral, because the drug works by relaxing arteriolar smooth muscle, resulting in vasodilation.

Mexiteline is an orally administered analog of intravenously administered lidocaine, and both drugs are class 1B antiarrhythmic agents that function by blocking sodium channels and interfering with nerve conduction. Their actions might be through central, peripheral, or mixed mechanisms, although more recent evidence suggests a central mechanism of action for these drugs.12,13 The exact mechanism through which these medications produce analgesia or in some cases provide prolonged remission and cure is unclear. Of interest, mutations in regions of chromosome 2q containing a cluster of sodium channel genes have been identified among patients with primary erythromelalgia.14 One of these mutations involves a voltage-regulated sodium channel expressed mainly in sensory and sympathetic neurons, which may play an important role in nociception and vasomotor control.

Lidocaine and mexiletine have been useful in the treatment of refractory chronic pain states associated with diabetic neuropathy,13,15,16 adiposis dolorosa,17 and a miscellaneous group of chronic pain conditions.18 A good response to lidocaine infusion has been predictive of success with mexiletine therapy. In studies on pain associated with diabetic neuropathy, the most appropriate dosage regimen appeared to be 450 mg/day. This dosage has the best therapeutic effect, with minimal side effects and no cardiovascular effects.15 Evidence also indicates that mexiletine therapy is most beneficial for patients with stabbing or burning pain, heat sensations, or formation.4 A later study of diabetic neuropathy showed a significant reduction in sleep disturbances and nocturnal pain symptoms with mexiletine.16 However, no correlation was found between mexiletine plasma concentrations and either therapeutic or adverse effects. The dosage of mexiletine is started at lower levels and gradually increased.

Because our patient’s condition was refractory to all other treatments, with only epidural analgesia providing some relief, we opted to try mexiletine. We found that our patient had a positive response to lidocaine infusion, once we achieved therapeutic lidocaine levels, and a good response to orally administered mexiletine. Once the maximal mexiletine dosage was reached (150 mg, 3 times daily), the patient and his family readily transitioned to self-administration and have maintained good adherence to this regimen.

REFERENCES

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