

Lidocaine patch for pain of erythromelalgia.

By Mark D. P. Davis, MB, MRCPI; Paola Sandroni, MD, PhD

Departments of Dermatology and Neurology, Mayo Clinic, Rochester, Minn.

Arch Dermatology/ Vol. 138, Jan 2002

REPORT OF A CASE

A 15-year-old white girl had continuous mild discomfort associated with coolness and slight cyanosis of both feet. Intermittently, whenever she exercised, her feet became bright red and extremely painful, consistent with intermittent episodes of erythromelalgia (Figure 1). The discomfort markedly affected her daily activities: she stopped hiking, playing sports, marching in the high school band, and attending physical education classes. She could walk for only 10 minutes in the local shopping mall before her feet became red, hot, and too painful to continue walking. The vascular studies (described in detail elsewhere¹) performed included measurement of (1) blood pressure in affected extremities, (2) transcutaneous oxygen, and (3) temperature in the lower limb and digits. Because the patient's symptoms were not elicited during these studies, the findings were unremarkable.

Neurophysiologic testing (described in detail elsewhere¹) included nerve conduction studies, needle electromyography, and an autonomic reflex screen. The autonomic reflex screen included a quantitative sudomotor axon reflex test (QSART), heart rate response to deep breathing and Valsalva maneuver, and adrenergic function testing. The QSART assesses the integrity of both the axon reflex arch and sweat glands in the dermis. Acetylcholine is iontophoresed into 1 compartment, and sweat output is measured from a different compartment. A solution of 10% acetylcholine is injected into the first compartment and a constant current of 2 mA is applied for 5 minutes. Sweat output is measured for 5 minutes after stimulus discontinuation. The results showed a diffuse but patchy small-fiber neuropathy with marked anhidrosis of the lower extremities.

The patient's symptoms did not respond to fulldose, prolonged trials of aspirin (325 mg daily for 4 months), an α -adrenergic blocker (doxazosin mesylate [Cardura; Pfizer-Roerig, New York, NY], 1 mg daily for 3 months), an anticonvulsant agent (gabapentin [Neurontin; Parke-Davis, Morris Plains, NJ]), a nonsteroidal antiinflammatory drug (50 mg of indomethacin, 3 times a day for 2 months), an oral antiarrhythmic agent (900 mg of mexiletine for 1 month; treatment was stopped because of gastrointestinal distress), and a tricyclic antidepressant drug (100 mg of nortriptyline daily for 2-1/2 months).

THERAPEUTIC CHALLENGE

The primary challenge was to relieve the patient of her disabling symptoms. Secondary aims were to control the erythromelalgia and to minimize the systemic medications she was taking.

SOLUTION

A commercially available form of topical lidocaine (5% lidocaine patch [Lidoderm; Endo Pharmaceuticals Inc, Chadds Ford, Pa]) recently became available and is indicated for relief of pain associated with postherpetic neuralgia. (Lidoderm is manufactured by Teikoku Seiyaku Co Ltd, Sanbonmatsu, Kagawa, Japan, for Endo Pharmaceuticals and is a registered trademark of Hind Health Care, Inc, San Jose, Calif.) We decided to use it to treat our patient's erythromelalgia.

The 5% lidocaine patch consists of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate film release liner. The release liner is removed before the patch is applied to the skin. Each adhesive patch, 10 X 14 cm, contains 700 mg of lidocaine (50 mg of lidocaine per gram of adhesive) in an aqueous base.

The 5% lidocaine patch was applied to the dorsum of the feet where the pain was at its maximum (Figure 2); as recommended by the manufacturer, it was removed after 12 hours. Almost immediately after placement, the patient experienced relief from her discomfort, both at rest and on exertion. This symptomatic improvement was sustained as long as the lidocaine patch was worn; however, the improvement waned over 2 to 3 hours after the patch was removed. Because the patient complained of pain predominantly during the daytime when she was exercising, the lidocaine patch was applied during the daytime and then removed at night. Cautiously, she increased her level of activity, and within 2 weeks after the patch was first applied, she was able to run around the track at school for the first time in a year, to play a game of soccer, to return to physical education class, to walk in the shopping mall for as long as 55 minutes, and to march in the high school band. If she overdid the activities, the pain still became intense enough to make her stop, but overall, the pain had improved remarkably. The patient tried to stop wearing the lidocaine patch, but her symptoms returned within 2 to 3 hours after the patch was removed.

It has to be noted that, although the patient was without pain, she continued to have signs of erythromelalgia; with the same amount of exertion as before the patch treatment, the erythema and heat occurred. The lidocaine patch did not produce any adverse effects, either local or systemic, during 5 months of follow-up.

CO
MM
ENT

Eryt
hro
mela
lgia
is a
rare



Figure 1. Bright red legs and feet during an episode of erythromelalgia.



Figure 2. Feet with lidocaine patch. The patch relieved the pain but not the redness and heat of the erythromelalgia.

clinical syndrome most often characterized by intermittent (although sometimes constant) bouts of painful, bright red, hot hands or feet. Frequently, the bouts are provoked by exercise or increased ambient temperature. Herein, we describe the occurrence of disabling erythromelalgia in a young girl that was unresponsive to several treatments. However, excellent pain relief was provided by topical lidocaine patches.

The pain of erythromelalgia is frequently disabling, and patients often obtain relief by lowering skin temperature (e.g., by applying cold objects to the affected area, exposing the affected extremities to cold surfaces, or immersing the limb in ice water) or by elevating the affected extremity. Frequently, these measures damage the skin, further exacerbating the pain, and occasionally cause maceration and problems associated with "immersion foot" (trench foot). The pain usually is described as hot, burning, or numb, and it may be severe and disabling. Davis et al[2] surveyed 98 patients who had erythromelalgia and reported statistically significant decreased quality of life scores in all 8 health domains as measured by a short-form 36-item survey.

Erythromelalgia may be difficult to treat.[2] It is likely that erythromelalgia represents a heterogeneous group of diseases that have a common clinical presentation and, hence, varying responses to medications. Indeed, in a survey of 99 patients with erythromelalgia [2] it was found that 84 different types of medications and treatments had been used, most of which provided no or only partial symptomatic relief. Each patient had taken many medications in an attempt to relieve the symptoms.

Patient response to erythromelalgia therapy is notoriously variable.[3] Some patients experience long-term pain control with either topical or oral monotherapy with antidepressants, anticonvulsants, or opioids, whereas in others the disease is extraordinarily refractory to all measures. Current approaches to treatment include tricyclic antidepressants, anticonvulsants, local anesthetics, clonidine, and opioids. If monotherapy fails, a mechanism- or symptom-based (or both) multi-drug regimen can be used. Intravenous and topical lidocaine, intravenous ketamine, carbamazepine, opioids, and, more recently, gabapentin have been used.[4]

Whether the primary cause of the pain in erythromelalgia is vasculopathic or neuropathic is debated. Sandroni et al recently reported that a high proportion of patients with erythromelalgia have distal small-fiber neuropathy with selective involvement of cutaneous sympathetic fibers; in addition, large-fiber neuropathy is often present. They also found a decrease in oxygenation of the affected areas during the period of symptoms despite an increase in blood flow and temperature in the affected area during the same

period. To explain this, researchers have hypothesized that shunting is occurring.[5,6] Thus, the pain may be attributable to the hypoxemia of the skin or the small-fiber neuropathy or both.

Irritable nociceptors are likely involved in the transmission of pain impulses of erythromelalgia. Irritable nociceptors are involved in at least a subpopulation of patients with postherpetic neuralgia, and a lidocaine patch can safely and effectively relieve the pain in these patients.[7,8] Neuropathic pain has distinct clinical pictures. The irritable nociceptor type of neuropathic pain is associated with a minimal sensory deficit, warm skin, and marked allodynia (ie, pain induced by an innocuous stimulus). Local skin block provides relief. Although primary afferent nociceptors are injured in irritable nociceptor pain, they still function. Damaged nerve fibers or terminals can generate ectopic impulses, and certain voltage-gated sodium channels, including PN3, are reported to be overexpressed after nerve injury, thus increasing current density and decreasing action potential threshold. This spontaneous activity contributes substantially to neuropathic pain.

The 5% lidocaine patch consists of an adhesive material containing 5% lidocaine, a chemical designated as an acetamide, 2(diethylamino)-N-(2,6-dimethylphenyl) with an octanol:water partition ratio of 43 at pH 7.4. Lidocaine is an amide-type local anesthetic agent that may stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.[9] The penetration of lidocaine into intact skin after application of the 5% lidocaine patch is sufficient to produce an analgesic effect, but the amount is less than is necessary to produce a complete sensory block. When the patch is used according to the recommended dosing instructions, only 3%±2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of the lidocaine remains in a used patch. The mean peak blood concentration of lidocaine is about 0.13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Findings after repeated application of 3 patches simultaneously for 12 hours (recommended maximum daily dose) once a day for 3 days indicated that the lidocaine concentration does not increase with daily use.

The 5% lidocaine patch is contraindicated for patients with a known sensitivity to local anesthetics of the amide type or to any other component of the product. The patch should be applied only to intact skin.

Although toxic effects of lidocaine may occur, the highest blood level of lidocaine measured in a study of 35 patients was 0.1 µg/mL,[10] indicating minimal systemic absorption of the drug. Also, the lidocaine patch did not produce any systemic adverse effects, and it was well tolerated when applied to allodynic skin for 12 hours.[8,10] Allergic contact dermatitis has not been reported for the lidocaine, patch, but it is a possibility. Also, patients may have a reaction to the adhesive material on the patch.

The topical lidocaine patch is a novel therapy that recently became available for postherpetic neuralgia, for which it is as effective as antidepressants, opioids, or gabapentin and safe for long-term use.[7,8] Of 32 patients who used the patch for longer than 3 years, most said it was the only treatment that substantially relieved postherpetic pain.[7] No systemic adverse effects have been reported.

Because patients with erythromelalgia have neuropathy, and irritable nociceptors may contribute to the pain of erythromelalgia, we decided to treat the symptoms of our patient with a lidocaine patch. This treatment provided her considerable symptomatic relief.

Increasing clinical evidence supports the use of topical analgesics in the treatment of postherpetic neuralgia, and this treatment may be extended to erythromelalgia. With lidocaine patch treatment, our patient experienced dramatic relief from pain and had a return to an almost normal level of activity. We therefore propose that lidocaine patches may be useful for local control of the pain associated with erythromelalgia. Treatment with topical lidocaine patches should be studied to determine their role in erythromelalgia and other conditions causing localized pain. This treatment may be a safe and simple option for controlling local pain of other conditions.

Accepted for publication May 25, 2001. Corresponding author. Mark D. P. Davis, MB, MRCPI, Departments of Dermatology and Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905

davis.mark@mayo.edu

REFERENCES

1. Sandroni P, Davis MDP, Harper CM Jr, et al. Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. *J Clin Neuromusc Dis.* 1999;1: 57-63.
2. Davis MD, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia: presentation and outcome in 168 patients. *Arch Dermatol.* 2000;136: 330-336.
3. Cohen JS. Erythromelalgia: new theories and new therapies. *J Am Acad Dermatol.* 2000;43:841-847.
4. Bonezzi C, Demartini L. Treatment options in postherpetic neuralgia. *Acta Neurol Scand Suppl.* 1999;173:25-35.
5. Kvemebo K. Erythromelalgia—a condition caused by microvascular arteriovenous shunting. *Vasa.* 1998;27:3-39.
6. Mork C, Asker CL, Salerud EG, Kvernebo K. Microvascular arteriovenous shunting is a probable pathogenetic mechanism in erythromelalgia. *J Invest Dermatol.* 2000;114:643-646.
7. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain.* 1999;80:533-538.
8. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. *Ann Neurol.* 1995;37:246-253.
9. Brau ME, Vogel W, Hempelmann G. Fundamental properties of local anesthetics: half-maximal blocking concentrations for tonic block of Na⁺ and K⁺ channels in peripheral nerve. *Anesth Analg.* 1998;87:885-889.
10. Rowbotham MC, Davies PS, Verkempinck C, Geier BS. Lidocaine patch: double-blind controlled study of a new treatment method for postherpetic neuralgia. *Pain.* 1996;65:39-44.