Combination gel of 1% amitriptyline and 0.5% ketamine to treat refractory erythromelalgia pain: a new treatment option?

by Paola Sandroni, MD, PhD; Mark D. P. Davis, MD
Departments of Neurology (Dr Sandroni) and Dermatology (Dr Davis), Mayo Clinic, Rochester, Minn

---

Arch Dermatol. 2006;142:283-286.

New Treatment Option?

REPORT OF A CASE

A 17-year-old white woman presented with a 2-year history of increasingly frequent episodes of erythromelalgia involving her hands, feet, and lower legs. She described the discomfort as "throbbing, burning, stinging." Her symptoms occurred daily. The episodes involved her feet about 10 to 15 times during the day and involved her hands slightly less frequently. Whenever her feet got warm at night, erythromelalgia developed. These episodes were extremely painful. Generally, the erythema and pain occurred independently in the hands and feet. The symptoms were precipitated in her hands and feet by exercise; for example, walking precipitated the symptoms in her feet and legs, and writing precipitated them in her hands. Occasionally, the symptoms occurred when she was at rest, and they occasionally were worse at night. The symptoms lasted from minutes to up to 2 hours. She relieved the symptoms by cooling the affected area with ice and by raising the symptomatic limbs above the level of her heart. At night, she would stick her feet out of bed to relieve the symptoms and, during warm weather, used a fan.

The symptoms markedly affected the patient's lifestyle. Because the symptoms flared with any activity, she avoided many daily activities, including going to the gym. When she went to a shopping mall, painful episodes developed after a short time, and she would have to sit down or walk very slowly. She missed days at school because of the symptoms. She had no underlying disease or diagnosis apart from attention-deficit/hyperactivity disorder, for which she had been receiving treatment with methylphenidate hydrochloride for the past 10 years. There was no family history of erythromelalgia.

Vascular laboratory testing documented the erythromelalgia by demonstrating the expected rise in temperature, which increased from a mean of 18.9°C in her toes without symptoms to approximately 23°C to 24°C with symptoms. This increase occurred

concomitantly with bright redness of the skin and a marked increase in blood flow as measured with laser Doppler ultrasonography. In the upper extremities, the temperature was low (21°C) in her fingers during the asymptomatic stage but increased to approximately 33°C with symptoms; there was increased blood flow, similar to that in her toes, without a notable change in transcutaneous oximetry measurements. No evidence of underlying disease was discovered, particularly no evidence of myeloproliferative disease. Although the antinuclear antibody titer was increased, the patient had no sign of an underlying connective tissue disease. The results of neurologic investigations, including assessment of large- and small-fiber nerves with electromyography, nerve conduction studies, and autonomic reflex screen (quantitative sudomotor axon reflex testing) were within reference ranges.

The erythromelalgia did not respond to treatment with aspirin or misoprostol. Although gabapentin therapy improved the symptoms slightly, it made the patient dizzy. Lidocaine patches had been quite helpful (she wore them all night and before exercising), but many of her normal daily activities continued to be severely curtailed. She gave up all sports at school and stopped attending dancing class. The temperature inside her house was kept between 70°F and 72°F. When she arrived home, she changed into shorts. She wore sandals only, no shoes or socks. At night, she avoided covering her legs with a blanket. She preferred to walk on cold tile floors. When she wrote, the erythromelalgia occasionally became worse, and this interfered with her schoolwork. Her mother photocopied articles that we provided on erythromelalgia and gave them to her daughter's teachers. Because of the erythromelalgia, the patient was given extended time for school examinations.

When the patient visited Hawaii the summer before being evaluated by us, her episodes of erythromelalgia were more intense and frequent because of the hot weather. She wore lidocaine patches the entire time she was in Hawaii.

When the patient became concerned about attending her high school formal dance, her mother suggested she stand in the snow barefoot if the symptoms flared in her feet.

THERAPEUTIC CHALLENGE

Treatment of erythromelalgia is difficult and often unsuccessful. For this young woman, we wanted a treatment that would help control the symptoms and allow her to return to her normal daily activities, namely, to be able to wear shoes and socks, attend the high school formal dance, sleep at night, and participate in school activities. We preferred to avoid systemic medication if possible.

SOLUTION

We prescribed a combination of topical 1% amitriptyline hydrochloride and 0.5% ketamine hydrochloride to be applied up to 4 or 5 times daily. Two days after this

treatment was initiated, the patient reported "spectacular improvement" in her symptoms after applying the combination medication twice daily. She had slept through the night for the first time in 2 years. She had walked through a large shopping mall for 8 hours with her mother. She and her mother were thrilled with the response and said it was the best medication she had tried. They estimated that the symptoms had improved 90%. At follow-up 2 months later, the patient reported that, before going to school, she applied the gel to her hands and feet. This permitted her to engage in the normal activities of the school day. She was able to write and walk without pain. Her episodes of erythromelalgia occurred with approximately the same frequency, but she was able to tolerate them. She has been cautious about returning to gym class but plans to do so. She attended her high school formal dance and wore shoes but did kick them off later in the evening because the auditorium had a cold tile floor.

COMMENT

Erythromelalgia is a clinical syndrome characterized by attacks in which the affected limbs become bright red, hot, and excruciatingly painful. The common trigger is heat exposure induced by exercise or increased ambient temperature. As the condition progresses, the limbs become permanently red, hot, and painful.1-3

The pain of erythromelalgia, commonly described as hot and burning in quality, is frequently disabling, and patients obtain relief by lowering skin temperature, for example, by applying cold objects to the affected area, exposing the affected extremities to cold surfaces, 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.

Pain associated with erythromelalgia may be difficult to treat. Because erythromelalgia is not a single disease but a syndrome, the response to various treatments may differ depending on the underlying condition and pathophysiology. Furthermore, treatment of the pain symptoms may have little if any effect on the other manifestations (ie, the redness and increased temperature of the affected limbs).

According to various theories, erythromelalgia is a vascular disorder or neuropathic condition.2 In previous studies,2 we have shown that both systems are involved, but we do not know which one is affected first. It is plausible that the vascular and neuropathic components differ in each subject depending on the underlying cause.4

Thus, the pain in erythromelalgia may be caused by relative hypoxia despite the high rate of blood flow to the limb, because of the inability to properly extract or use oxygen (as in inflammatory conditions, mitochondrial dysfunction, or toxic exposure), or by severe inflammation or small-fiber dysfunction. All these mechanisms may contribute in each case, making treatment even more complex; hence, patients often require a rational multidrug strategy to control the pain.

Indeed, according to a survey1 of 99 patients with erythromelalgia, they had used 84 different types of medications and treatments, most of which provided no or only partial symptomatic relief. Each patient had taken many medications to relieve the symptoms.1, 3

Patient response to erythromelalgia therapy is notoriously variable. Some patients experience long-term pain control with topical agents such as lidocaine, oral anti-inflammatory agents, prostaglandin (misoprostol), vasoactive agents, neuromodulating drugs (ie, antidepressants, anticonvulsants, or antiarrhythmics), or opioids, whereas in other patients the disease is extraordinarily refractory to all measures.

Irritable nociceptors are likely involved in the maintenance of pain in erythromelalgia. The extreme sensitiveness of the skin (ie, allodynia) in these patients clearly supports this concept. However, it does not explain the complexity of the pain, which most likely involves central sensitization. Recent evidence 5-7 indicates that altered hyperexcitable sodium channels are expressed in inherited painful neuropathies and inherited erythromelalgia. Consequently, we attempted to treat other patients with a topical local anesthetic and had varying success.8

However, every treatment at our disposal seemed to fail in some patients. Therefore, we decided to use a combination cream or gel of amitriptyline and ketamine in pluronic lecithin organogel. This vehicle has been described as ideal for transdermal preparations because it disrupts the lipid layer of the stratum corneum, thus favoring the absorption of topically applied medications.9

Amitriptyline, a first-generation tricyclic antidepressant, works by inhibiting serotonin and noradrenaline reuptake; it also blocks sodium channels. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptors have a key role in the maintenance of chronic pain syndromes. Normally, after a single painful stimulus, only glutamatergic -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are activated. However, when a barrage of impulses reaches the dorsal horn, the neuron does not have time to repolarize properly. The NMDA receptors have a magnesium molecule that normally blocks the channel, but when the intracellular potential rises and the neuron remains depolarized for a prolonged period (as with rapid glutamatergic firing), the magnesium molecule is dislodged, thus opening the channel to the influx of calcium and further depolarizing the cell. The influx of calcium activates second messengers and promotes the transcription of various genes, resulting in the increased production of glutamate and other excitatory neurotransmitters and the expression of supersensitive subtypes of sodium channels in primary sensory neurons. This cascade of events leads to increased excitability of the neurons of the pain pathways; thus, painful stimulation continues (the wind-up phenomenon).

We speculate that topical application of the combination gel of 1% amitriptyline and 0.5% ketamine works by numerous mechanisms:

1. Ketamine blocks NMDA receptors located on the peripheral terminals of primary nociceptive afferents.10

2. Ketamine may be taken up by the nerve terminals and transported orthodromically to the dorsal root ganglia and dorsal horn. Thus, NMDA receptors at both sites can be blocked.

3. Although ketamine is primarily an NMDA antagonist, it may be able to modulate other glutamatergic receptors, AMPA and kainate, further reducing the discharges from primary nociceptive afferents.

4. Sodium channel blockade by amitriptyline prevents excessive nociceptor discharge by blocking the action potential, similar to a local anesthetic such as lidocaine (which is more potent than amitriptyline). Furthermore, there is evidence that sodium channels are involved in modulating NMDA receptors; thus, amitriptyline too could possibly act indirectly on NMDA receptors.

It is less clear how the serotonin and noradrenalin reuptake inhibitor effect of amitriptyline works topically because at the peripheral level it would be expected to enhance pain sensation. We speculate that amitriptyline may work through central modulation after being transported orthodromically in the axon to the dorsal root ganglia and dorsal horn.

Systemic absorption has not been studied systematically, but we measured the blood levels of ketamine in 2 subjects after topical application, and it was undetectable. Hence, we assume that topical application is safe, probably even when applied to a large surface area of skin. Until additional pharmacodynamic studies have been completed, caution is strongly advised because of the potential psychoactive adverse effects of ketamine.

Although the response from our first group of patients treated with combination gel has been dramatic, larger-scale studies are needed to evaluate response rate systematically. We emphasize, however, that the 5 patients described in the table are among the most severely affected. Furthermore, it is too early to determine whether tolerance or tachyphylaxis will be a factor with prolonged use. Nonetheless, this strategy offers the flexibility of easy application, no systemic adverse effects, and the possibility of combining it with other treatment options without concern of drug interactions. The combination gel has to be compounded by a pharmacist, which may be a problem for some patients, but it seems to be fairly easy to do and at a much lower cost than for most treatments commonly used.

Although we expected no effect on the other manifestations of erythromelalgia, specifically the redness and high temperature of the affected limbs, 2 patients noticed improvement in those symptoms also, possibly through a decrease in neurogenic inflammation or modulation of efferent nerve fibers to skin vessels (or both). Thus, our topical treatment is a desirable alternative for erythromelalgia symptoms refractory to other treatment.

Submissions

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the manuscript number (eg, Fig1_DCE00001.jpg). Material must be accompanied by the required copyright transfer statement (see Instructions for Authors). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com).

AUTHOR INFORMATION

Correspondence: Paola Sandroni, MD, PhD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (psandroni@mayo.edu).

Accepted for Publication: June 9, 2005.

Financial Disclosure: None.

REFERENCES

1. 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.

2. 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.

3. Cohen JS. Erythromelalgia: new theories and new therapies. J Am Acad Dermatol. 2000;43:841-847.

4. Orstavik K, Mork C, Kvernebo K, Jorum E. Pain in primary erythromelalgia: a neuropathic component? Pain. 2004;110:531-538.

5. Cummins TR, Dib-Hajj SD, Waxman SG. Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy. J Neurosci. 2004;24:8232-8236.

6. Drenth JP, Finley WH, Breedveld GJ, et al. The primary erythermalgia-susceptibility gene is located on chromosome 2q31-32. Am J Hum Genet. 2001;68:1277-1282.

7. Yang Y, Wang Y, Li S, et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet. 2004;41:171-174.

8. Davis MD, Sandroni P. Lidocaine patch for pain of erythromelalgia. Arch Dermatol. 2002;138:17-19.

9. The history of pluronic lecithin organogel: an interview with Marty Jones. Int J Pharm Compounding. 2003;7:180-184.

10. Carlton SM, Zhou S, Coggeshall RE. Evidence for the interaction of glutamate and NK1 receptors in the periphery. Brain Res. 1998;790:160-169.