THE TREATMENT OF ERYTHROMELALGIA

Jay S. Cohen M.D.

The purpose of this article is to provide information regarding the variety of therapies that can be used for treating erythromelalgia. Erythromelalgia is a rare disorder that typically affects the skin of the feet or hands, or both, and causes visible redness (erythema), pain, and a sensation of intense heat. The skin of other areas such as the legs, arms, ears or nose may also be affected. Erythromelalgia often looks like a severe sunburn. To the patient, the skin feels hot and burns. Indeed, erythromelalgia is one of the most painful disorders on earth. Mild symptoms often impair normal activities such as walking, standing, working, socializing and exercising. Sleep may also be impaired. Severe symptoms cause constant pain and disability.

Erythromelalgia usually occurs bilaterally, but unilateral cases occur. The incidence and prevalence of erythromelalgia in the United States are unknown; however it is estimated that the incidence of erythromelalgia in Norway is 1/400,000. The pain of erythromelalgia is typically aggravated by heat and relieved by cold. To combat the pain, which can be severe, many people resort to extreme measures such as placing their legs (or arms) in ice water, which provides complete yet temporary pain relief. As the water warms, a painful rebound of symptoms occurs, so some people continue icing around the clock. This is a dangerous process, because excessive icing can lead to skin injury, maceration, gangrene and amputation. It is usually better to use a fan rather than ice water to cool the limbs.

Primary vs. Secondary Erythromelalgia

In most cases, the origin of the erythromelalgia is unknown. In such cases, the erythromelalgia is considered “primary.” “Secondary” cases occur with identifiable underlying causes. In secondary cases, the underlying disorders should be treated first, because this sometimes improves the erythromelalgia. For example, although aspirin is only occasionally effective for treating primary erythromelalgia, it can be dramatically effective for erythromelalgia secondary to blood disorders (polycythemia, thrombocytopenia, thrombocytopenia,
leukemia).\textsuperscript{4,5} Corticosteroids are sometimes helpful in erythromelalgia secondary to autoimmune disorders or acute small fiber sensory neuropathies (nerve injuries).\textsuperscript{6-9} Any medications a person is taking should be evaluated as a possible etiologic agent for triggering erythromelalgia. All vasodilating substances should be discontinued, if possible.

Sometimes, secondary erythromelalgia does not improve with treatment of the primary disorder. In such cases, secondary erythromelalgia should be treated the same as primary erythromelalgia. In this article, the term erythromelalgia refers to the primary form.

THERAPEUTIC CONSIDERATIONS

In “evidence-based” medicine, evidence is defined as knowledge from research and clinical experience.\textsuperscript{10} Since few formal clinical studies have been published regarding erythromelalgia, our knowledge is based mainly on reports of cases, surveys, and clinical experience. This article contains information from published reports, as well as data from The Erythromelalgia Association (TEA) 2003 survey on the effectiveness of various therapies (Table 1).\textsuperscript{11} The TEA survey data represents the self-reported medication responses of TEA members, primarily people with chronic erythromelalgia, many of whom have not obtained adequate benefit from treatment. As such, the survey findings may be skewed toward unfavorable results. Please take this into consideration when reviewing the survey findings.

This article also contains information from the author's own 12-year experience with erythromelalgia (severe disability, remission, relapse, good control). The author was a longtime board member of TEA, and over the years he has been consulted by more than 100 people with erythromelalgia and 30 healthcare practitioners seeking advice about treatment.

A remarkable degree of variability is seen in people’s responses to various therapies. Therapies that help some people may be ineffective or worsen symptoms in others. No one medication is reliably effective for all erythromelalgia sufferers. Combination therapy is sometimes more effective than single drug therapy.

Some people with erythromelalgia appear to be highly sensitive to the therapeutic and adverse effects of medications. These individuals should be started with the lowest doses available of therapeutic agents. Others may require full doses of the same drugs. Fortunately, when an effective therapy is started, the response may be apparent quickly. If improvement with a new therapy is not seen within 1-2 weeks, the dosage should be increased gradually. Improvement is an indication for further use of a drug, whereas adverse effects or worsening of symptoms require discontinuance. The lack of response suggests that the medication dosage should be increased.
FIRST LINE THERAPIES

In my experience, four types of therapies can be considered the most effective for treating erythromelalgia.

Transdermal Therapy with Amitriptyline and Ketamine

The simplest and perhaps safest approach to treating erythromelalgia is a transdermal cream containing 1% amitriptyline and 0.5% ketamine. The cream is applied over the skin affected by the erythromelalgia. The combination of ketamine and amitriptyline are believed to reduce pain, thereby freeing users to function normally despite the fact the redness and other vascular changes may continue. Results are usually seen within days. Preliminary results from the Mayo Clinic suggest an improvement rate of 50% to 70%. This therapy can be ordered by doctors from compounding pharmacies (for pharmacy locations: www.iacprx.org).

Serotonin-Norepinephrine and Serotonin Reuptake Inhibitors

SNRIs and SSRIs provide substantial benefit for some erythromelalgia patients. The medication reported in the medical literature most often to produce marked improvement or remission in erythromelalgia is venlafaxine (Effexor), a SNRI. Through 2007, fourteen such cases (5 remissions) had been reported. The TEA survey (Table 1) offers a different picture. Of 50 respondents to the TEA survey, none obtained complete relief and 52 percent experienced no relief or worsened with venlafaxine. Even at low doses, nausea can be a problem with venlafaxine. Still, because the drug has been reported to produce benefit or complete remission in some patients, venlafaxine is considered a first line drug for treating erythromelalgia.

Benefit has also been reported with other serotonin enhancing medications including sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), and tramadol (Ultram). For those who do not respond or worsen with venlafaxine or SSRIs, duloxetine (Cymbalta, a SNRI) and maprotiline (Ludiomil, NRI) may be tried. There have been several informal reports of benefit from duloxetine.

In broader context, it appears that serotonin may be a key factor in some cases of erythromelalgia. The effects of serotonin on vascular tissue may produce vasodilation or vasoconstriction. This may explain why some erythromelalgia sufferers respond favorably to serotonergic agents, while others show no response or worsen.

Gabapentin (Neurontin)

Four reports of complete remission with gabapentin have been published. According to the TEA survey, 60% of individuals trying gabapentin obtained some degree of improvement. Response is usually seen at the standard initial dose of 300 mg four times daily, but some users experience marked sedation or reduced mental acuity and may do better initially at 100 mg three times daily. In one reported case, an 89 year-old woman was started with 100 mg three times daily of gabapentin and gradually titrated to 300 mg, three times daily, at which dosage remission occurred. Other people may need higher doses of gabapentin. In many cases, gabapentin reduces pain but has little effect on vascular symptomatology (redness, swelling, heat intolerance).
Calcium Channel Antagonists

When the therapies listed above are not helpful, the calcium channel antagonists may be effective. Initial reports of improvement of erythromelalgia with calcium channel antagonist therapies were surprising. Calcium channel antagonists are vasodilators, and there are many reports of calcium channel antagonists (nifedipine, verapamil, nicardipine) precipitating erythromelalgia. However, in 1996 Belch et al. reported improvement in some cases of erythromelalgia using nifedipine. Subsequently, there have been reports of substantial improvement or remission with calcium channel antagonists. Yet, because calcium channel antagonists may also worsen erythromelalgia, these drugs must be used cautiously with close supervision. For example, a test dose of 30 mg of short-acting diltiazem might be used initially.

Magnesium is the body's natural calcium channel antagonist and has multiple effects on vascular activity. Magnesium has been reported to produce improvement in cases of erythromelalgia. However, as with other calcium channel antagonists, some individuals obtain no benefit or worsen with magnesium. The recommended daily amount of magnesium is about 400 mg/day, but for erythromelalgia therapeutic doses range up to 1,000 mg/day or more. Best results are obtained with well-absorbed forms such as magnesium chelate or liquid magnesium citrate solutions. Magnesium therapy requires normal kidney function and good hydration, and use in the elderly or dosing above the RDA necessitates close medical supervision.

The TEA survey indicates that 21%-39% of people taking calcium antagonists obtained some degree of improvement with diltiazem, amlodipine, or magnesium. The best results occurred with magnesium: 29/75 (39%) obtained some improvement. Worsening occurred in 17/43 (40%) of patients receiving diltiazem, 9/23 (40%) receiving amlodipine, and 12/75 (16%) magnesium. Overall, these survey numbers are not overly impressive, yet when improvement occurs with calcium channel antagonists, it can be considerable.

People taking magnesium or prescription calcium channel antagonists often know within hours or days whether these interventions are helpful. If helpful, the dosage may be increased gradually to maximum effect. If the erythromelalgia worsens, discontinue immediately.

Other substances reported to have calcium channel antagonist effects are chromium, alpha lipoic acid, high doses of ascorbic acid, and the herb butterbur. Cyclosporine, an immunosuppressant drug with calcium channel antagonist properties, was reported to produce improvement in a patient with severe erythromelalgia. Another report described cyclosporine as triggering erythromelalgia, which resolved when the drug was stopped. The side effects of cyclosporine preclude its use as a standard treatment for erythromelalgia.

SECOND LINE THERAPIES

The following therapies have been reported to provide varying degrees of benefit in people with erythromelalgia. Therapies are listed in the author's general order of preference, but practitioners should choose among them based on the clinical characteristics of each case as well as the practitioner's familiarity with the therapies.

Propranolol

A case published in 1977 described a remission of erythromelalgia with propranolol 10 mg three times daily. Results from the TEA survey indicate that most people receiving propranolol obtain minimal to moderate improvement. Relatively few persons reported no improvement or worsening. Propranolol's effect may lie in its ability to block beta-adrenergic vasodilator nerves in the skin.
Interestingly, an occasional complaint of people receiving propranolol for hypertension is cold hands and feet. A Raynauds-like response, which may provide desirable cooling in erythromelalgia, is seen less frequently with other beta-blockers. Thus, in the author's opinion, propranolol is the beta-blocker of choice for treating erythromelalgia.

**Serotonin Antagonists**

Serotonin antagonists are logical choices in people whose erythromelalgia does not respond to SNRIs or SSRIs. Cyproheptadine and pizotifen are antihistamines with proven serotonin antagonist effects at 5-HT2 receptors. Published reports describe two remissions with cyproheptadine (12 mg/day and 24 mg/day) and three cases with marked improvement using pizotifen (Sandomigran) (not available in the U.S.) In its June 2006 newsletter, TEA reported a remission that has lasted 10 years with a low dose of cyproheptadine. Other serotonin antagonists include the herbs feverfew and white willow. Only one unpublished report supports the herbs’ benefit in erythromelalgia. Both of these herbs exert their effects at 5-HT2 receptors, and both have shown efficacy in treating migraine headaches, which have clinical similarities to erythromelalgia.

**Antihistamines**

Traditional antihistamines may be useful in some cases of erythromelalgia. The TEA survey indicates that approximately 40 percent of users obtain modest improvement in their erythromelalgia, whereas 60 percent do not obtain improvement. One TEA member reported marked improvement with variable use of desloratadine, chlorpheniramine, and diphenhydramine.

**Tricyclic Antidepressants**

Long known to provide benefit for neuropathies, tricyclics are sometimes helpful in erythromelalgia. One case of remission can be found in the medical literature. In Table 1, 40 percent of using amitriptyline obtained modest benefit in their erythromelalgia, and 60 percent showed no improvement or worsened. Results were similar for imipramine except that 1/11 (9%) reported complete relief. Many individuals are sensitive to the sedating and anticholinergic adverse effects of tricyclic drugs, so low initial doses might be considered.

**Acetylsalicylic Acid (Aspirin, ASA)**

Although ASA is rapidly effective for erythromelalgia secondary to hematologic (blood) disorders (polycythemia, thrombocythemia, leukemia), it is only occasionally helpful for other types of erythromelalgia. The results in Table 1 support this viewpoint. Practitioners should note that standard doses of ASA (325-650 mg four times daily) may be necessary to benefit some individuals. Those responsive to ASA should be evaluated for an underlying hematologic disorder.

**Other CNS Medications**

Davis et al. reported on 5 individuals receiving mexiletine: in 2 the drug was somewhat helpful, and in 3 it was not helpful. One case report described improvement in a person with primary erythromelalgia with mexiletine. The literature contains one report of erythromelalgia associated with lupus that responded to clonazepam. In the TEA survey, people receiving clonazepam or carbamazepine reported modest results.
Prostaglandins

European studies have reported oral misoprostol and intravenous prostaglandin E1 to be effective for pain and vascular symptoms of erythromelalgia. Results for misoprostol from the TEA survey are less impressive. Of nine subjects, only two (22%) reported any degree of improvement. The remaining 78 percent reported no improvement or worsening.

Opioids

In the TEA survey, 22 of 32 persons (69%) receiving oral opioids reported some degree of improvement. Ten of 32 (31%) reported no improvement or worsening with opioids. In many cases, opioids provide pain relief without improvement of vascular symptoms.

TRANSDERMAL THERAPIES

Transdermal gels containing 1% amitriptyline and 0.5% ketamine have been tested on five erythromelalgia patients. Self-rated improvement was 95%, 90%, 70%, 50% and 0%. These are promising results.

Lidocaine patches applied every 12 hours have been reported to provide pain relief, although this therapy does not alter vascular symptoms. Capsaicin therapy with epidural anesthesia has been reported as helpful in erythromelalgia, but TEA members who sought this treatment have reported mixed results. Table 1 lists 44 people who have tried over-the-counter capsaicin cream, and 31 (70%) reported a worsening of their erythromelalgia. For this reason, I do not recommend self-administered capsaicin therapy as a treatment for erythromelalgia.

PROCEDURES

Sympathetic blocks and epidurals can be helpful in treating some cases of erythromelalgia, yet they appear to be underutilized. In those who improve with sympathetic blocks, a series of blocks should be tried. Zoppi et al. reported 2 cases of remission and 1 of improvement following 10 daily sympathetic blocks (alternating left and right at sympathetic chains at L2-4). The literature contains reports of remission with sympathectomy, but careful case selection is imperative before this procedure is performed. Sympathectomy should be considered only for those whose erythromelalgia improves with blocks. Conversely, if a sympathetic block causes worsening of a person's erythromelalgia, treatment should be discontinued. Sympathectomy should not be considered for such persons because of the risk of permanent worsening of erythromelalgia symptoms.

Morphine pumps and spinal cord stimulators have been used with some benefit in erythromelalgia. The TEA survey lists better results with the morphine pump. These methods may help control pain, although they do not seem to improve vascular symptoms.

Intravenous lidocaine, with or without mexiletine, has been reported effective in 3 cases.

TREATMENT OF CHILDREN AND ADOLESCENTS

Many of the therapies discussed above may also be considered for children with erythromelalgia. Amitriptyline/ketamine transdermal gel was tried in a 17 year old with good results. Remissions in children or adolescents have been reported with magnesium and gabapentin. Combination therapy is sometimes more effective than monotherapy. In a 4-year-old girl who developed erythromelalgia following influenza vaccination, rapid resolution was obtained with low-dose aspirin, carbamazepine and propranolol.
Long-term epidurals have produced improvement in pain and vascular symptoms in severe cases. Intravenous nitroprusside, which is contraindicated in adults because it can worsen erythromelalgia, has been used effectively in children and adolescents.

DISCUSSION

Recent research has demonstrated abnormal vascular activity and excessive shunting of the blood in erythromelalgic areas of the skin. Davis et al. have shown that neuropathies (nerve injuries) underlie many cases of erythromelalgia. Yet, many questions remain.

Perhaps the most persistent question I have heard from people is: What is erythromelalgia? Enough information has accrued to hazard an answer. First, the rapid responses of erythromelalgic skin areas to heat and cold exposure are distinctive. Warm ambient temperature can quickly trigger erythromelalgia symptoms, whereas exposure to cold (e.g., ice water) rapidly suppresses all symptoms. Cold exposure serves as a complete antidote. In 1997, Kalgard et al. suggested that erythromelalgia is not a distinct disease, but a reversible dysfunction of the vasculature. Based on the response to heat and cold, erythromelalgia may represent a dysfunction of the body's normal skin response to heat.

In hyperthermia, massive vasodilation in the heat exchange areas of the skin is a normal physiological response. Hyperthermia skin reactions are triggered by increases in internal body temperature, as occurs from hot ambient temperatures or intense exercise. In hyperthermia, resting skin blood flow can increase 24-32 times normal, from a flow of 250 ml/min. to 6 to 8 liter/min. Initially, the increased flow is mediated by beta adrenergic, but the main vasodilator is nitric oxide, the major mediator of endothelium dependent vasodilation. Tellingly, these are the very same stimuli, and nitric oxide is the same mediator, that trigger flaring in erythromelalgia, yet at much lower temperatures. In erythromelalgia, it appears that a dysfunctional heat response system in the skin reacts to mild stimuli of warmth as if hyperthermia were occurring. This would explain the paroxysmal, massive vasodilation that is characteristic of erythromelalgia, as well as the rapid, complete control of symptoms with cooling.

Although this hypothesis requires further study, the concept of a dysfunctional hyperthermia mechanism makes sense clinically, and it offers a way for patients and doctors to understand this baffling and often frightening disorder, erythromelalgia.

CONCLUSION

Erythromelalgia is a rare disorder that can cause severe pain and disability even in its moderate forms. Treatment methods have improved considerably over recent years, and today, based on clinical experience, case reports and surveys, many people can be helped. This article provides information for people suffering from erythromelalgia and their physicians to consider for treating erythromelalgia. Cautious, stepwise treatment can often lead to significant improvement.

ACKNOWLEDGMENT

I would like to thank The Erythromelalgia Association (TEA) for access to its 2003 survey. TEA is an excellent resource for information, published articles, and support for people with erythromelalgia as well as their friends, families, and health care professionals. Readers can obtain information about membership and resources at www.erythromelalgia.org.
NOTE TO READERS: The purpose of this article is solely informational and educational. The information herein should not be considered to be a substitute for the direct medical advice of your doctor, nor is it meant to encourage the diagnosis or treatment of any illness, disease, or other medical problem by laypersons. If you are under a physician's care for any condition, he or she can advise you whether the information in this article is suitable for you. Readers should not make any changes in drugs, doses, or any other aspects of their medical treatment unless specifically directed to do so by their own doctors.

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**Devices and Procedures**

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<td>Magnets</td>
<td>26</td>
<td>3 (12%)</td>
<td>18 (79%)</td>
<td>5 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine Pump</td>
<td>5</td>
<td>2 (40%)</td>
<td>2 (40%)</td>
<td>1 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Stimulation</td>
<td>11</td>
<td>1 (9%)</td>
<td>3 (27%)</td>
<td>6 (55%)</td>
<td>1 (9%)</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


55. Sandroni P, Davis MD. Combination gel of 1% amitriptyline and 0.5% ketamine to treat refractory erythromelalgia pain. A New Treatment Option? Arch Dermatol 2006;142:283-6.