Topical amitriptyline combined with ketamine for the treatment of erythromelalgia: A retrospective study of 36 patients at Mayo Clinic

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Abstract
Objectives: To assess the response of erythromelalgia to compounded topical amitriptyline-ketamine
Design: Retrospective study
Setting: Single academic medical center
Patients: This study evaluated 60 patients with erythromelalgia who were prescribed compounded topical amitriptyline-ketamine from 2004-2011.
Main Outcome Measure: Relief of pain due to application of topical amitriptyline-ketamine
Results: Follow-up information on medication efficacy was available for 36 patients, of whom 32 (89%) were female. The mean age was 44.7 years old, with a standard deviation of 15.8 and a range of 5-74. Patients used the medication 1-6 times per day, with a mean of 4.1. Of the 36 patients, 1 (3%) had complete relief from symptoms, 14 (39%) had significant relief, 12 (33%) had some relief, 7 (19%) experienced no relief, and 2 (6%) had local worsening of symptoms. No patients experienced systemic side effects.
Conclusions: A majority (75%) of patients with erythromelalgia reported improvement in their pain with the use of a combination of amitriptyline and ketamine in a topical formulation; the medication was well tolerated.

Introduction

Erythromelalgia is an uncommon neurovascular disorder characterized by redness, increased temperature, and pain that usually occurs in the extremities. It is a heterogenous disorder, with a wide variation in severity and age and time course of onset[1]. In addition, it has been reported to occur in areas other than the extremities, including ears, nose, face, and neck[2]. Patients with erythromelalgia have higher morbidity and mortality than age-matched controls and are at increased risk for myeloproliferative disorders[1].

Treatment for erythromelalgia remains challenging, with varying response to medical therapy resulting in a trial-and-error approach to treatment of the disorder. Treatments that have been reported to be used for erythromelalgia include aspirin, non-steroidal antiinflammatory drugs, opioids, beta blockers, antihistamines, vasodilators, anticonvulsants, antidepressants, clonidine, oral and topical corticosteroids, topical lidocaine, mexiletine, and misoprostol, among others. However, according to a retrospective study by Davis et al. of 2000 patients, few of these treatments were consistently effective[1].

Recent advances have been made in the understanding of the biochemical basis of erythromelalgia. Specific sodium channel mutations have been identified in the pathogenesis of inherited erythromelalgia. Specifically, mutations in SCN9A cause membrane hyperexcitability in sensory neurons and has been associated with familial erythromelalgia[3]. This has encouraged study into compounds that block sodium channels and development of new treatments that could provide relief for these patients[4]. Medications currently used that block sodium channels include mexiletine and topical lidocaine, class 1b antiarrhythmics[5, 6].

In 2006, Drs. Sandroni and Davis reported success in treatment of erythromelalgia using topical amitriptyline-ketamine in 4 out of 5 cases studied[7]. When applied topically, amitriptyline acts primarily as a sodium channel blocker to dull neuropathic pain. In addition, ketamine has bene hypothesized to act through a number of pathways, including NMDA, AMPA, and kainate receptors. These medications may act synergistically to limit transmission of painful stimuli. In addition, these same biochemical effects may prevent vasodilation, reducing the characteristic redness and warmth of the disorder.

To evaluate the use of topical amitriptyline-ketamine in a larger sample size, we retrospectively studied patients with erythromelalgia who had been treated since 2004 at Mayo Clinic. This study was approved by the institutional review board.

Methods:

Identification of patients

This retrospective study identified 1,031 patients who had received compounded topical amitriptyline-ketamine for various disorders from 2004 to 2011 through the Mayo Clinic Pharmacy. The medical records of these patients were reviewed to identify diagnosis for which the medication was prescribed, presenting symptoms, relief, side effects, and demographic information. Patients for whom the topical medication was prescribed for erythromelalgia were reviewed again to ensure patients met diagnostic criteria (episodes of redness, increased temperature, and pain), location of body affected, previous and adjunctive treatments, and presence and type of neuropathy present.

Follow-up was determined by reviewing the medical records for documentation of a response to the treatment prescribed.

Patient descriptions of relief were graded using the following scale: complete relief, significant relief (defined as >50% or wording used to indicate significant relief was made), some relief (<50% relief or relief without a specific grade), no improvement, and worsening of symptoms. The study data was managed using research electronic data capture tools hosted at Mayo Clinic.

Statistics

Comparisons among study groups were done using Fisher exact or Chi-squared tests. Clinical characteristics of the patients, such as presence of small fiber neuropathy and disease distribution, were analyzed to determine potential association with positive clinical outcome. P values less than 0.05 were considered statistically significant.

Results:

Of the 1,031 patients studied who received topical amitriptyline-ketamine since 2004, 60 of them were prescribed the medication for erythromelalgia. Of those 60 patients, follow-up information on efficacy was available for 36 (60%). Of the 36 patients, 32 (89%) were female. The mean age of the patients was 44.7, median 47.8, standard deviation 15.8, and a range of 5-74 years. The formulations of medication used in these 36 patients are included in table 1.

Of the 36 patients with follow-up information, 1 (3%) had complete relief from symptoms, 14 (39%) had significant relief, 12 (33%) had some relief, 7 (19%) experienced no relief, and 2 (6%) had local worsening of symptoms. The only side effects that were recorded were 1 patient whose face was made redder with application of the medication and another patient who developed worsening of the Raynaud's phenomenon associated with the patient's erythromelalgia. No systemic side effects were noted.

Of the 36 patients, the distribution of disease was as follows: 35 lower extremities, 22 hands or upper extremities, 6 face, 5 ears, 1 trunk, and 1 neck (numbers add up to more than 36 because many patients had symptoms at more than one site). 24 (67%) patients demonstrated small fiber neuropathy via characteristic symptoms of autonomic dysfunction or autonomic testing such as sweat testing. In addition, 3 (8%) patients had large fiber and 2 (6%) had motor fiber neuropathy, all of whom also had a small fiber neuropathy. Patients had used or were using a broad range of medical therapies to treat their erythromelalgia, including aspirin, gabapentin, clonidine, antidepressants (including amitriptyline), opioids, non-opioid analgesics, benzodiazepines, atypical anti-psychotics, mexiletine, misoprostol, oral and topical corticosteroids, and lidocaine patch.

Statistical testing of presence of small fiber neuropathy vs. relief following application of the combination topical did not reveal a statistically significant association [table 2]. In addition, no association was found between body distribution of the erythromelalgia and relief with the topical [table 2].

Comment:

This study identified 60 patients who were prescribed amitriptyline-ketamine for the treatment of erythromelalgia. The 36 patients for whom follow-up was available had positive responses to the medication; 27 (75%) had any level of relief and 15 (42%) experienced complete or significant relief of symptoms. Statistical analysis revealed no predictors of relief, including presence of small fiber neuropathy and body distribution. In addition, the medication was well-tolerated, with only 2 patients experiencing local and none having systemic side effects. The two side effects that did occur seem to be related to the underlying neurovascular disturbances and were relieved following discontinuation of the medication. With three-quarters of patients experiencing relief in this study with a relatively low side effect burden, topical amitriptyline-ketamine is potentially one of the more efficacious treatments known for erythromelalgia.

Treatment of erythromelalgia is challenging in medical practice, with a broad range of therapies having unpredictable treatment response. The data from Davis et. al in their 2000 survey of patients with erythromelalgia shows that no individual treatment consistently provided a high level of relief in the majority of patients[1]. In addition, multiple treatments were usually required to attain an appropriate level of relief. The patients in the present study often used multiple medications, but some of the patients were able to obtain significant relief using only the combination topical. Given that patients with erythromelalgia often suffer a large burden of systemic side effects from their medications, topical medications can have favorable side effect and drug interaction profiles.

This study has a number of limitations related to its retrospective nature. First, a uniform system for recording the severity of symptoms and the degree of symptom relief was not used. Second, follow-up was not available for a substantial number of patients with erythromelalgia who were prescribed the combination topical (24/60). Third, patients were often taking a variety of other treatments, and this study is not able distinguish between relief related to the combination topical and other treatments. Fourth, the concentrations and vehicle used for the topical were not standardized: a number of formulations and concentrations of the two drugs were used in the topical formulation.

In conclusion, patients with erythromelalgia had decreased pain with the use of topical amitriptyline-ketamine and the medication was well tolerated. With the very high response rate seen in this study, the combination topical may be an effective first-line treatment for erythromelalgia. However, clinical trials must be conducted to firmly establish the appropriate treatment course in patients with erythromelalgia.

Table 1: Medication use and formulation, N(%) unless otherwise specified

Daily uses, mean (SD); Median (range)	4.1 (1.2); 5 (1-6)
1% amitriptyline/ 0.5% ketamine	
PLO gel	17 (47)
Vanicream	12 (33)
2% amitriptyline/ 0.5% ketamine	
PLO gel	0 (0)
Vanicream	4 (11)
2% amitriptyline/ 0.5% ketamine/ 2% lidocaine	
PLO gel	3 (8)
Vanicream	0 (0)

Table 2: Association between relief using topical amitriptyline-ketamine and presence of small fiber neuropathy and erythromelalgia involvement of hands or face

Relief using amitriptyline-ketamine topical	Presence of small fiber neuropathy		P Value
	Yes (n=55)	No (n=32)	
			0.69
No	7 (19)	2 (6)	
Yes	18 (50)	9 (25)	
	Involvement of hands or face		
	Yes (n=7)	No (n=78)	
			0.33
No	3 (8)	6 (17)	
Yes	4 (11)	23 (64)	

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