Letters

RESEARCH LETTER

Topically Applied Midodrine, 0.2%, an α_1-Agonist, for the Treatment of Erythromelalgia

We report the response of patients with erythromelalgia to topical midodrine hydrochloride, an α_1-agonist. Erythromelalgia is a rare syndrome characterized by red, hot, painful feet and hands, sometimes extending proximally. Episodes are generally intermittent, lasting from minutes to hours, but can be continuous.[1] Although numerous therapeutic regimens have been described,[2] none is universally effective. Since symptoms are generally localized, topical treatments might be preferable to avoid systemic adverse effects.[3-5]

Among the proposed mechanisms for erythromelalgia is local vasodilatation since increased blood flow has been observed in Doppler studies. During symptoms, we have noted that the mean temperature of the toe skin increased by 7.8°C, and blood flow increased 10.2-fold.[1,4]

Because vasodilatation may account for the flushing during an episode, the use of a vasoconstrictor seems reasonable. We hypothesized that midodrine, a vasoactive drug that causes vasoconstriction, might be effective. Midodrine, a peripherally acting α_1-agonist, activates the α-adrenergic receptors of vessels, resulting in increased vascular tone and reduced blood volume. A patient with erythromelalgia responding to oral midodrine has been reported.[6]

We used a topical preparation of midodrine for the management of erythromelalgia. We then reviewed reported outcomes among patients with erythromelalgia who received treatment with topically applied midodrine, 0.2%.

Methods | This study was conducted from November 1, 2011, to November 1, 2013, and was approved by the Mayo Clinic Institutional Review Board. Participants were patients in the Department of Dermatology at Mayo Clinic in Rochester, Minnesota, and provided written informed consent. The clinical diagnosis was erythromelalgia; midodrine, 0.2%, was to be applied topically, and patients were available for follow-up. *Erythromelalgia* was defined as the occurrence of red, hot, painful feet or hands. Midodrine, 0.2%, in a moisturizing skin cream (Vanicream) was compounded at the Mayo Clinic pharmacy and applied topically 3 times daily during symptoms.

After the diagnosis was confirmed, data were abstracted on demographics, adverse effects, and pain level before treatment. Using a verbal rating scale, the patient chose words to describe the sensory qualities of the pain and the overall experience of the pain. Each word chosen was assigned a rank value and these values were used to determine the pain rating index that ranges from 0 (no pain) to 5 (excruciating pain). Response to medication was graded as complete relief, substantial relief (≥50% relief or marked relief), some relief (<50% relief), no change, or worsening of symptoms. The grading scale was defined for the purposes of the study, and the data were derived from interpretation of descriptions in the medical record of how patients reported responding to midodrine, 0.2%.

Further information was obtained from documentation of follow-up visits to the department of dermatology after use of midodrine, 0.2%. Blood pressure was monitored in 2 patients before and after midodrine was prescribed.

Table. Summary of Data for 12 Patients

Characteristic	No. (%)
Age, mean (range), y	57 (26-79)
Female sex	9 (75)
White race[a]	11 (92)
Pain level before medication[b]	
Severe	10 (83)
Moderate	1 (8)
Range of improvement (relief)	
Complete	0
Substantial	4 (33)
Some	7 (58)
None	1 (8)
Worsening of symptoms	0
Adverse effects of midodrine hydrochloride, 2%	
Nonspecific gastrointestinal tract discomfort	1 (8)
Increase in blood pressure[c]	1 (8)
Prior treatment	
Gabapentin	4 (33)
Trazodone hydrochloride	1 (8)
Combination gel amitriptyline, 2%, and ketamine, 0.5%	9 (75)

[a] The race/ethnicity of 1 patient (8%) was unknown.

[b] The level of pain was not documented for 1 patient (8%).

[c] The increase was documented in 1 of 2 patients whose blood pressure was measured consistently.

Results | Topical midodrine, 0.2%, was prescribed for 12 patients with erythromelalgia (**Table**). Most patients had received previously prescribed treatments with no substantial improvement. Of the 2 patients whose blood pressure was monitored before and after application of midodrine, 0.2%, prescription, 1 had no significant changes, but the other had an increase in blood pressure. Ten patients (83%) responded to therapy within minutes (not quantified).

Discussion | In this study, we summarized self-reported responses to a topical preparation of midodrine, 0.2%, that was used as needed. All but 1 patient reported improvement. Topical midodrine, 0.2%, was well tolerated; only 2 of the 12 patients (17%) reported adverse effects.

This study had limitations. The sample with available follow-up was small, available follow-up was documented in the

medical record but was not standardized, the follow-up criterion of interest was "general improvement" in erythromelalgia without obtaining further details, and many patients were using other medications. Nonetheless, these results suggest that a topical preparation of midodrine, 0.2%, is well tolerated and improves symptoms of erythromelalgia. Further investigation is warranted.

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