

Nitroprusside treatment of erythromelalgia in an adolescent female.

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OBJECTIVE: To report a case of erythromelalgia in an adolescent patient successfully treated with nitroprusside.

CASE SUMMARY: A 15-year-old girl with erythromelalgia resistant to aspirin therapy received an infusion of nitroprusside. The response of the erythromelalgia to nitroprusside was dramatic, with complete pain resolution within 17 hours after the start of therapy. No relapse of erythromelalgia was seen when nitroprusside was discontinued and the patient remained well after 6 months.

DISCUSSION: This case adds to existing literature substantiating the benefit of nitroprusside for the treatment of erythromelalgia in pediatric patients. Erythromelalgia in children may represent a different disease entity than that seen in adults, which is commonly responsive to aspirin therapy. The pathogenesis of erythromelalgia is unclear and precludes formulating a proposed mechanism by which nitroprusside has benefit in children.

CONCLUSIONS: Nitroprusside is valuable for erythromelalgia resistant to aspirin

therapy in pediatric patients. Because of unanswered questions regarding the disease, aspirin remains the agent of first choice in all patients with this rare disease.

KEY WORDS: nitroprusside, erythromelalgia.

ERYTHROMELALGIA, also known as erythermalgia, is a rare disorder in which the patient experiences intense burning pain, elevated temperature, and erythema in the extremities. Symptoms of the disease are worsened by heat and relieved by cooling the skin and limb elevation.[1] The disease has traditionally and most often been grouped into primary or secondary forms. Primary idiopathic erythromelalgia, in contrast to the secondary form, is not associated with another disease process and occurs in approximately 60% of adults with the disease.[2] Pediatric patients have been considered to have the primary disease, leading to a recommendation that it be reclassified as adult-onset, with primary and secondary types, and early-onset (childhood) forms.[3]

While aspirin has been shown to provide effective relief for almost all adult patients with secondary erythromelalgia associated with myeloproliferative disease, the treatment of choice for primary erythromelalgia in adult or pediatric patients is not well established.[1,5] Nitroprusside has been used in children in whom aspirin therapy was ineffective.[4-9] We describe an adolescent with apparent primary erythromelalgia successfully treated with nitroprusside.

CASE REPORT

A 15-year-old white girl was transferred on July 22, 1995, to a rehabilitation unit following a 10-day acute care hospitalization for treatment of erythromelalgia. The onset of erythromelalgia dated to mid-June, when the patient developed general arthralgia, followed by symmetric reddening, itching, and burning pain in her feet and subsequently her hands. Her medical history was unremarkable and her only recent illness was an upper respiratory tract infection with cough. Rheumatic, infectious, and orthopedic diseases were ruled out and laboratory results included a normal complete blood count, coagulation studies, erythrocyte sedimentation rate, and α -galactosidase A concentration, and a negative antinuclear antibody test.

The patient was prescribed various oral analgesics (including aspirin, nonsteroidal anti-inflammatory agents, hydrocodone, meperidine), clonidine, and mild sedatives by her pediatrician before hospitalization for intractable pain. On admission, she was almost totally bedridden and had decreased appetite with weight loss. Partial improvement in the patient's pain was attained only after initiation of intravenous morphine and midazolam infusions, in addition to constant ice and cooling packs to her hands and feet. On transfer to the rehabilitation unit, she was receiving morphine extended-release 60 mg bid, hydroxyzine 50 mg q4h, amitriptyline 75 mg Its, clonidine 0.4 mg/d, doxazosin 1 mg bid, carbamazepine 200 mg q8h (for neuropathic pain), aspirin 325 mg/d, and sertraline 50 mg/d (for perceived unusual pain response and fluctuating moods).

Physical rehabilitation was complicated by continued intractable pain and sedation believed attributable to large dosages of narcotics. The patient's vital signs were stable; the systolic BP ranged from 90 to 124 mm Hg and diastolic BP between 68 and 90 mm Hg. Based on a medical literature review and professional communication, the decision was made to initiate nitroprusside therapy on August 7. Initial titration of the intravenous nitroprusside infusion to a targeted rate of 2 µg/kg/min resulted in a lowered BP of 83/39 mm Hg; the dosage was decreased to 1 µg/kg/min with a resultant BP of 108/72 mm Hg after 10 minutes at the lower dosage. Patient-reported pain ratings (scale of 0 = none to 5 = worst imaginable pain) were implemented at the initiation of nitroprusside and were 1 at 1 hour, 3 at 5 hours, 2 at 7 hours, and 0 at 17 hours and thereafter. Also, the patient was refusing all other pain and antianxiety medications during this time.

After less than 24 hours of nitroprusside therapy, the temperature of the cooling pads was slowly elevated without patient discomfort, and no erythema was noted on her hands or feet. The nitroprusside dosage was increased to 1.5 µg/kg/min after 24 hours of the lower dosage without hypotension; the dosage was tapered over a total 64-hour period (total dose 206.4 mg). There was no further pain, nor were any medications needed to control the erythromelgia. Nausea and occasional emesis that were present before the initiation of nitroprusside therapy were treated as needed with ondansetron, and anxiety attributed to narcotic withdrawal was treated with lorazepam. The patient was experiencing only mild muscle pain and stiffness associated with prolonged immobilization when she was discharged home for continued mobilization and strengthening on August 11. A 6-month follow-up examination revealed complete resolution of the erythromelgia; she required no further pharmacotherapy during this time period.

DISCUSSION

Erythromelgia is a rare disease that often is described as treatment-resistant.[3] Neither the clinical types nor the underlying pathogenesis of erythromelgia are known with certainty. The disease has traditionally been classified as primary idiopathic and secondary types [2] The secondary form of the disease commonly occurs in adults, has been more extensively studied, and usually responds to pharmacotherapy with aspirin [3] Indeed, Michiels et al [5] suggested that relief from aspirin is the most accurate diagnostic test for secondary erythromelgia.[5] Moreover, many patients diagnosed with primary or idiopathic erythromelgia will later prove to have the secondary form of the disease, as an associated myeloproliferative disease commonly has its onset months to years after the onset of erythromelgia symptoms[3]

However, classification of erythromelgia has been questioned. Kurzrock and Cohen[3] recommended reclassification of erythromelgia to adult- and early-onset forms. According to these investigators, early-onset erythromelgia occurs in childhood and adolescence, is predominant in girls, most often affects lower extremities in bilateral fashion, and is typically resistant to treatment with aspirin. Adult-onset erythromelgia includes primary idiopathic (60% of patients) and secondary forms, more commonly

affects men, is often asymmetric, and usually responds to aspirin therapy. The adolescent patient in our case is well described by the early-onset classification.

More recently, Drenth et al,[4] have proposed that pediatric patients, similar to adults, actually experience a secondary form of the disease entity named erythermalgia, which occurs in association with the underlying disease of hypertension. They suggested the disorder was uniformly resistant to aspirin and that nitroprusside may be the drug of choice. Primary erythermalgia was described as a congenital disorder that persists throughout life, without a specific treatment. Finally, Drenth et al. suggested the two types of erythermalgia are different from erythromelalgia, which occurs only in adults and is associated with thrombocytopenia.

It should be noted that hypertension has long been known to be associated with secondary erythromelalgia, and that mixed results have been obtained with the use of various antihypertensive medications.[14] Our patient did not demonstrate elevated blood pressure before nitroprusside treatment during hospitalization in the rehabilitation unit, but data were not available from the patient's initial presentation to the pediatrician who later initiated clonidine therapy.

It is unclear whether different types of erythromelalgia have different pathophysiologic bases. Histopathologic data support involvement of platelet aggregation in patients with secondary erythromelalgia associated with thrombocytopenia; the efficacy of aspirin in these patients may further substantiate a role for platelet aggregation.[5] In the study by Michiels et al.,[5] aspirin, which causes irreversible inhibition of platelet aggregation, offered prolonged improvement in the symptoms of erythromelalgia, while indomethacin, which causes transient platelet inhibition, provided relief for only a few hours. In contrast, much less is known regarding the underlying pathogenesis of primary erythromelalgia. A recent study of two pediatric patients with proposed primary erythromelalgia by Rauck et al[9] corroborated previous findings[3] of increased blood flow in the extremities of the patients; it is suggested that shunting of blood away from the capillary level may occur, resulting in peripheral vascular ischemia.

Nevertheless, it is clear that whatever classification scheme for this disease is most accurate, the pathogenesis of the disease in children remains unknown.[10] It also remains unclear whether different types of erythromelalgia have different pathologic etiologies.[2,3,9] Many patients diagnosed with primary disease later prove to have secondary disease.[1] As such, aspirin would seem to be the logical initial pharmacotherapy in all patients presenting with erythromelalgia; initial aspirin therapy may relieve symptoms in about 70% of all patients with erythromelalgia.[2]

Unsuccessful treatment with aspirin in patients with erythromelalgia has resulted in the use of other modalities including nitroprusside. Previous reports[6-8] of success with this agent in pediatric erythromelalgia prompted its use in our patient. The mechanism of action of nitroprusside to provide benefit in patients with erythromelalgia is understandably unknown in consideration of questions surrounding the pathogenesis of the disease.[9] Nitroprusside has direct action on vascular smooth muscle to cause

vasodilation, presumably via release of nitric oxide.[10] Interestingly, nitric oxide also has inhibitory effects on platelet aggregation.[11] Thus, the logic of the use of nitroprusside is consistent with prevailing, albeit incomplete, pathogenic theories of erythromelalgia. However, it is important to note that nitroprusside has not always been of benefit in similar pediatric patients, and variable results have been obtained with other antihypertensive medications.[4,7,9] Interestingly, to our knowledge, nitroglycerin has not been evaluated for this purpose.

The response of erythromelalgia to nitroprusside in our patient revealed similar characteristics to those in prior reported cases

Table 1: Characteristics of Nitroprusside-Treated Erythromelalgia

REFERENCE	AGE (y) (sex)	DISEASE BEFORE TREATMENT	TIME TO RESPONSE (h)	DOSAGE OF NP AT RESPONSE	DURATION OF NP (d)
Drenth et al. (1995)[4]	17 (F)	4 wk	ND	ND	ND
Özsoylu et al. (1979)[6]	9 (F)	3 d	48 for pain; 72 for redness	3 µg/kg/min at response; 5 µg/kg/min maximum	8
Kvernebo and Seem (1987)[7]	8 (F) 16 (F)	7 wk 15 d	96 no response	ND ND	5 6
Özsoylu and Coskun (1984)[8]	15 (M) 1.5 (F)	10d 6 d	3 24 for redness; 120 for HBP	1 µg/kg/min 1 µg/kg/min 5 µg/kg/min maximum	2 5
Rauck et al. (1996)[9]	17 (M) 17 (F)	<4 wk 4 wk	72 (partial) ND	4 µg/kg/min maximum ND	3 ND
Present case	15 (F)	7 wk	17	1 µg/kg/min	2-67

HBP = high blood pressure; ND = data not available; NP = nitroprusside.

(Table 1).[4,6-9] The clinical response was rapid, occurring over the first few days in all patients who responded. Rebound of erythromelalgia symptoms did not occur on discontinuation of nitroprusside.[6-8] Moreover, a relatively low dosage of nitroprusside is typically required, thereby minimizing accumulation of cyanide and its associated toxicity. [6,8,12] Such characteristics make nitroprusside a therapeutic alternative that can be safely attempted with appropriate monitoring and that may offer a potentially dramatic effect.

The pharmacologic characteristics of nitroprusside in association with pharmacotherapeutic aspects of existing case reports indicates it should be considered a valuable therapeutic option in the treatment of erythromelalgia resistant to aspirin therapy. At the present time, data regarding this rare disease are insufficient to suggest nitroprusside should be a drug of first choice for erythromelalgia in pediatric patients.

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