Efficacy of Oral Nifedipine in the Treatment of Reflex Sympathetic Dystrophy

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Reflex sympathetic dystrophy (RSD), is a common posttraumatic pain syndrome for which no reliably effective oral form of therapy has been found. Oral therapy has been attempted with steroids, tricyclic antidepressants, beta-blockers, and antiseizure medications, none of which are predictably helpful.1-5 Multiple invasive treatments, including sympathetic blockade and iv regional local anesthetic, reserpine, or guanethidine blocks, have been employed, but again with inconsistent success.6-9 Transcutaneous nerve stimulation is effective in some patients10 but aggravates symptoms in others.11

Following a report of the use of oral nifedipine in the treatment of Raynaud's phenomenon,12 a syndrome that, like RSD, is characterized by vasospasm and cold intolerance, we studied the ability of orally administered nifedipine to relieve the symptoms of RSD.

METHODS

Thirteen patients were treated with nifedipine in an open-label study after they had given informed consent for a protocol approved by our institutional review board. The ages of the 10 female and three male patients ranged from 11 to 66 years (average—39 years). The patients first were interviewed by one of the study participants (D.S.P. or C.H.M.) when they had been referred with a probable diagnosis of RSD. Criteria for entry into the study included a clear history of trauma with the subsequent onset of pain characterized by one or more of the following: burning character, dyesthesias, cold intolerance, and trophic changes. A cold stress‡‡ test was obtained for most patients but was not a criterion for entry into the study. Nifedipine was

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Key words: Pain; causalgia; reflex sympathetic dystrophy; pharmacology; nifedipine.
<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Sex/Age</th>
<th>Pain Site*</th>
<th>Pain Duration</th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
<th>Effective Dosage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/57</td>
<td>RUE</td>
<td>4 months</td>
<td>VI†</td>
<td>Improved</td>
<td>10 mg tid</td>
<td>Pain-free 4 mos after treatment</td>
</tr>
<tr>
<td>2</td>
<td>M/32</td>
<td>RUE</td>
<td>6 weeks</td>
<td>VI†</td>
<td>Improved</td>
<td>20 mg tid</td>
<td>Pain-free 3 mos after treatment</td>
</tr>
<tr>
<td>3</td>
<td>F/11</td>
<td>RLE</td>
<td>2 months</td>
<td>VI</td>
<td>VI</td>
<td>20 mg tid</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F/51</td>
<td>RUE</td>
<td>18 months</td>
<td>VI</td>
<td>Improved</td>
<td>10 mg tid</td>
<td>Resumed employment</td>
</tr>
<tr>
<td>5</td>
<td>F/41</td>
<td>LLE</td>
<td>36 months</td>
<td>VI</td>
<td>Improved</td>
<td>10 mg tid</td>
<td>Burning thigh pain completely resolved; hip pain persisted</td>
</tr>
<tr>
<td>6</td>
<td>F/60</td>
<td>LUE</td>
<td>6 weeks</td>
<td>VI</td>
<td>Improved</td>
<td>20 mg tid</td>
<td>Died, intracranial metastasis</td>
</tr>
<tr>
<td>7</td>
<td>M/60</td>
<td>RUE</td>
<td>3 months</td>
<td>N</td>
<td>NA</td>
<td>10 mg tid</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M/32</td>
<td>RUE</td>
<td>24 months</td>
<td>N</td>
<td>NA‡</td>
<td>30 mg tid</td>
<td>Patient reports approx. 60% improvement; pain recurs with missed doses</td>
</tr>
<tr>
<td>9</td>
<td>F/34</td>
<td>RLE</td>
<td>14 years</td>
<td>VI</td>
<td>VI</td>
<td>20 mg tid</td>
<td>Patient reports 80% improvement</td>
</tr>
<tr>
<td>10</td>
<td>F/26</td>
<td>RUE</td>
<td>2 months</td>
<td>N</td>
<td>NA</td>
<td>10 mg tid</td>
<td>Successfully treated with guanethidine block</td>
</tr>
<tr>
<td>11</td>
<td>F/29</td>
<td>RUE</td>
<td>6 months</td>
<td>NA</td>
<td>NA</td>
<td>10 mg tid</td>
<td>No response after the 1 week on therapy</td>
</tr>
<tr>
<td>12</td>
<td>F/42</td>
<td>RUE</td>
<td>4 years</td>
<td>VI</td>
<td>NA</td>
<td>10 mg tid</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>F/66</td>
<td>RUE</td>
<td>5 months</td>
<td>VI</td>
<td>VI</td>
<td>20 mg tid</td>
<td>Pain recurred, persisted after reinstatement of drug</td>
</tr>
</tbody>
</table>

* UE = upper extremity; LE = lower extremity; R = right; L = left.
† VI = vasomotor instability; N = normal.
† NA = not available.

started at an oral dosage of 10 mg tid. If symptoms had not improved after 1 week, the dosage was increased to 20 mg tid. If symptoms had not improved after 3 weeks, the dosage was increased to 50 mg tid. Whenever partial improvement occurred, the dosage was continued for 2 weeks longer before being increased, if that increase was needed. When patients had achieved a stable level of pain relief for 3 weeks on a given dosage of nifedipine, the dosage was tapered over several days and discontinued. If pain recurred, oral therapy was reinstated. All patients were aware that alternative therapy for RSD was available and that they could request that therapy at any time.

**RESULTS**

The results and clinical characteristics for all 13 cases are summarized in table 1. Seven patients (patients 1–7) had complete relief of symptoms; two (patients 8 and 9) had partial relief; three withdrew because of headache (patients 10–12) (several other patients noted mild nausea but were able to continue therapy); and one patient (patient 13) failed to obtain relief from nifedipine therapy. Cold stress testing demonstrated vasomotor instability in nine of 12 patients before therapy. Therapy for the 13th patient had been started in another institution before cold stress testing could be obtained. Five of the nine patients with abnormal cold stress tests before therapy showed an improvement with nifedipine therapy. Two of the cold stress tests showing improved results were carried out after the patients had been weaned successfully from nifedipine.

Among three of the 10 patients who tolerated therapy, one (patient 7) died and two (patients 8 and 9) continued the medication for partial palliation of symptoms. The
medication was successfully withdrawn from three of the remaining seven patients (patients 1–3), and their symptoms did not return. The other four patients (patients 4–6, 13) noted recurrence of pain with weaning. In three of those four, nifedipine was reinstituted and the pain again resolved; in one (patient 13) the degree of pain relief obtained with the first course of therapy could not be duplicated. Due to difficulty in assessing her subjective reports, she was termed a treatment failure.

Representative Case Reports:

Case 1: A 57-year-old woman had pain of 4 months' duration in the area of her distal right ulna and right little finger following a fracture of the little finger. The pain was constant and burning, worsened by exposure to cold, and accompanied by edema; it was worse at night, virtually preventing sleep. Physical therapy had increased the pain, and analgesics and antidepressants had been ineffective. After 3 weeks of nifedipine therapy, 10 mg tid, the patient had complete resolution of pain. Nifedipine was discontinued without recurrence of pain during 4 months of follow-up study. Repeat cold stress testing showed resolution of vasomotor instability.

Case 4: A 51-year-old woman presented with right wrist and hand pain of 18 months' duration following minor trauma. Pain was intermittent and burning and was increased by cold and exercise. A cold stress test demonstrated vasomotor instability. Tricyclic antidepressants, analgesics, and intravenous reserpine blocks had all been tried but had failed to alleviate her discomfort. Pain was markedly decreased within 3 weeks of nifedipine therapy at a dosage of 20 mg tid. The dosage was then decreased to 10 mg tid. Eight weeks following initiation of the therapy, her pain had completely resolved and she had returned to work after 18 months of unemployment. Repeat cold stress testing showed complete resolution of vasomotor instability. An attempt to wean the patient from nifedipine was terminated when her symptoms recurred. She has remained on 10 mg tid with continued relief of symptoms for 6 months.

Case 13: A 66-year-old woman had pain of 5 months' duration following surgical correction of right carpal tunnel syndrome. The pain was described as aching; it was markedly aggravated by cold and exercise and was accompanied by edema. Cold stress testing demonstrated vasomotor instability. Analgesics and tricyclic antidepressants had been ineffective. After 1 week of oral nifedipine therapy, 10 mg tid, the patient noted decreased pain and swelling and increased mobility. The dosage of nifedipine was increased to 20 mg tid, and after 4 weeks of therapy complete absence of swelling and markedly increased flexibility and mobility of the hand were observed. One week after nifedipine was discontinued, the cold stress test was repeated and was still abnormal. Her pain returned when she resumed a vigorous manual activity (constant knitting), and subsequent therapy with nifedipine was unsuccessful. Although her symptoms and physical findings improved with the first course of therapy, her failure to respond to a second course of therapy, coupled with extreme difficulty in assessing her subjective response, prompted her placement in the treatment failure category.

DISCUSSION

RSD represents a spectrum of disorders, the symptoms of which may include pain, vasomotor disturbances, and trophic changes of the skin and underlying muscles, bones, and joints. 4-6 The syndrome is accompanied frequently by hyperesthesia, swelling, and severe disability. 4,5,7 The mechanism by which these symptoms are produced remains controversial. 5 Conventional treatment has consisted of physical therapy and sympathetic blocks of the affected extremity. 5,7 Recently, intravenous regional reserpine and guanethidine have been investigated as possible alternative therapies. 5,9 Improvements in skin temperature and in transtummataneous PO2 in the involved extremity and normalization of cold stress testing have accompanied subjective improvement when reserpine or guanethidine are used for regional intravascular sympathetic blockade. 14-16

These forms of therapy appear to improve the symptoms of RSD in part by inducing vasodilation in the involved area. A recent report suggests that phenoxymenzamine, another drug that produces peripheral vasodilation, is effective in the treatment of RSD. 17 Calcium entry blockers represent a means of inducing peripheral vasodilation without specifically interfering with the peripheral sympathetic nervous system. 18-20 Nifedipine, a calcium entry blocker, relaxes smooth muscle, 10 increases peripheral blood flow, 18 and antagonizes the effects of norepinephrine on arterial and venous smooth muscle. 19 These effects have been exploited in the treatment of Raynaud's phenomenon with moderate success. 19,21 The improvement in the cold stress test in five of the 13 cases reported here tends to support the hypothesis that treatment with nifedipine may not only interrupt the pain cycle but may also reverse signs of vasomotor instability.

The results in this series of patients, obtained in an open-label study, suggest that nifedipine may have a role as an orally effective therapeutic option. However, these results should be regarded as preliminary, pending appropriate double-blind cross-over confirmation, since the possibility of observer bias cannot be excluded. The failure of multiple previous therapeutic endeavors in these patients makes the occurrence of a placebo response to nifedipine unlikely. The effects appear to be relatively specific for RSD, rather than a nonspecific analgesic effect. We have had no success with nifedipine therapy in eight patients with chronic musculoskeletal pain following orthopedic procedures.

We conclude from these preliminary results that nifedipine therapy may offer potential as an alternative to traditional forms of therapy for the management of RSD, particularly in patients who prefer oral treatment to injections.

REFERENCES


Acute Obstruction of the Left Mainstem Bronchus Following An Attempted Nasotracheal Intubation: An Unusual Case Report

R. D. Seifert, D.O.,* M. Starnsic, M.D.,† D. Zwillingberg, M.D.‡

Several cases of unusual complications of endotracheal and nasotracheal intubation have been reported.1–5 Our case report demonstrates an unusual complication of nasotracheal intubation and a potential complication of any instrumentation of the nose (e.g., nasogastric tubes, temperature probes).

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Key words: Complications: epistaxis. Intubation, endotracheal: complications. Lung: aspiration.

REPORT OF A CASE

A 55-year-old man was admitted with a chief complaint of increasing right upper-extremity weakness. He had an 18-year history of multiple sclerosis with right lower extremity weakness that was also increasing in severity. A cervical myelogram showed cervical spondylosis, and a cervical laminectomy was performed from C3–C7 without incident. Induction of anesthesia and subsequent oral endotracheal intubation were uneventful. Three weeks later the patient developed urinary retention and was brought to the operating room for cystoscopy and possible transurethral resection of the prostate. Because a Philadelphia collar was in place, the neck was not to be extended. Regional anesthesia was not performed due to the recent change in neurologic status of his right lower extremity. General anesthesia via a mask was not performed because of potential airway management difficulties with mask fit and the inability to mobilize the neck and jaw freely.

Blind nasal intubation was planned under topical anesthesia with sedation. It was the policy of our institution at that time to utilize