Traumatic Dysesthesia of the Trigeminal Nerve

Dermot Canavan, B Dent Sc
Postdoctoral Resident
Department of Orofacial Pain
School of Dentistry
University of California, Los Angeles
Los Angeles, California

Steven B. Graff-Radford, DDS
Assistant Research Dentist
Department of Orofacial Pain
University of California, Los Angeles
School of Dentistry
and Director
The Pain Center
Cedars Sinai Medical Center
Los Angeles, California

Barton M. Gratt, DDS
Professor
Section of Oral Radiology
School of Dentistry
University of California, Los Angeles
Los Angeles, California

Correspondence to:
Dr Steven Graff-Radford
Department of Orofacial Pain
School of Dentistry
University of California, Los Angeles
CHS 43-009
Los Angeles, California 90024

Traumatic injury to the peripheral nerves often results in persistent discomfort. Substance P has been implicated as a mediator of pain, and depletion of this neurotransmitter has been shown to reduce pain. Subjects suffering from traumatic dysesthesia of the trigeminal nerve were treated with capsaicin, a substance P depleter with significant long-term effects. This form of therapy may be used individually or in combination with other pharmacologic interventions in the treatment of traumatic trigeminal dysesthesia.
J OROFACIAL PAIN 1994;8:391–396.

Traumatic injury of peripheral nerves in humans may result in pain, dysesthesias, paresthesias, and skeletomotor and autonomic disturbances.[1] These complaints are often self-limiting, but in a certain population, pain or discomfort may persist. This pain poses a significant clinical management problem. Dysesthesia is usually defined as an unpleasant abnormal sensation, either elicited or spontaneous.[2] Paresthesia, in contrast, has been defined as any abnormal sensation, such as burning, prickling, or formication, that is not unpleasant.[2] Both of these conditions are commonly associated with injury to sensory pathways in either the peripheral or central nervous system. The dysesthesia that accompanies traumatic injury to peripheral nerves has been attributed to deafferentation and hyperactivity of spinal/central pain transmission neurons.[3] Minor tissue damage associated with pain, without obvious nerve damage, may also lead to the development of the clinical characteristics of a neuropathy.[4]

Although large afferent fibers may show pathologic changes as a result of trauma, small unmyelinated fibers are invariably affected.[5] Traumatized afferent neurons may generate activity through four possible mechanisms: *(1)* neuroma; *(2)* neurogenic inflammation; *(3)* trauma; and *(4)* sympathetically maintained pain. Abnormal sensations resulting from neural injury are therefore the "consequence of disorder of the central control systems that establish the normal routing and amplification of sensory signals."[6,7]

Neurotransmitters are required for the ongoing activation and processing of nociception. Depending on the site of injury or the mechanism producing the pain, different neurotransmitters have been implicated. Substantial evidence exists implicating the neuropeptide substance P as one of the transmitters in nociceptive pathways.[8] It has been proposed that the release of substance P from nociceptors following tissue injury contributes to the spread of neurogenically mediated hyperalgesia and vasodilatation. Substance P, in combination with compounds released from dam-

aged tissues, can further sensitize or activate nociceptor afferents. Endogenous neuropeptides, particularly substance P,[9-11] have been implicated in the inflammation and pain of arthritic conditions.[12,13] In the rat model, substance-P–induced inflammation has been shown to be suppressed by capsaicin, which appears to deplete substance P receptors on target tissues. This effect is considered to be long lasting.[14] The principal source of capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is capsicum, the common pepper plant.[15]

Recent reports suggested that the depolarizing effect of capsaicin is selective for C-fiber polymodal nociceptor afferents and involves opening a nonselective cation channel.[16] Thus the selective nature of capsaicin's influence on C-fiber activity suggests that it may be useful in treating pain conditions triggered by C-fiber input. The efficacy of capsaicin in the management of postmastectomy pain syndrome,[17] postherpetic neuralgia,[18] cluster headaches,[19] diabetic neuropathy,[20] and phantom limb pain[21] has been evaluated.

Persistent dysesthesia following neural trauma has been reported as a complication of orthognathic surgery, implant placement, third-molar removal, endodontic therapy, and routine dental procedures.[22-25] The present report describes the use of capsaicin as an adjunctive treatment of postsurgical sensory disturbance involving the trigeminal nerve. The use of capsaicin was helpful in treating facial dysesthesia after trauma as in the three case reports presented.

Case 1

A 70-year-old woman, a retired school teacher, presented with bilateral mandibular stiffness in the mental nerve distribution. The stiffness was continuous and associated with pain of moderate intensity. The pain was aggravated by changes in temperature and relieved by ibuprofen. The problem started after the woman sustained a bilateral fractured mandible in the mental nerve region during a motor vehicle accident. Initially, a plastic surgeon reduced the fracture. She was then referred to a dentist who believed that a bone graft was necessary before the placement of dental implants. This was done by an oral surgeon who placed a stabilizing plate on the left side of the mandible. Later, three dental implants were placed to support a complete mandibular denture. The patient's jaw stiffness and pain had continued throughout this time. Because of the pain, the patient was unable to masticate properly on the right side. She was referred to The Pain Center, Cedars Sinai Medical Center, where a comprehensive clinical evaluation was carried out. The oral, stomatognathic (temporomandibular joint), myofascial, and cervical screening examinations were noncontributory. However, the neurologic screening examination revealed an area of increased sensitivity to light touch bilaterally in the mental nerve region which reproduced the complaint. The recommended therapy was a tricyclic antidepressant in combination with a topical capsaicin (Zostrix). Desipramine hydrochloride was started at 10 mg at bedtime and then gradually increased to 30 mg. It was initially suggested that the patient should apply the capsaicin cream five times a day in the affected area for 7 days, then three times a day for an additional 3 weeks. A topical anesthetic was offered in combination with the capsaicin to enhance compliance. At 1-year follow-up, the patient reported no pain and continued with 10 mg of nortriptyline hydrochloride and a single use of capsaicin per day.

Case 2

A 62-year-old woman, a homemaker, presented with bilateral continuous pain in her chin and jaw. The pain was variable in intensity, and at times she had a tingling tightness or burning sensation in her chin. The discomfort had been present for 2 years following surgery for mandibular advancement and mandibular osteotomy. No aggravating factors were described. Aspirin, ice, and heat had been tried with little benefit. She was referred to The Pain Center, Cedars Sinai Medical Center, where a comprehensive clinical evaluation was carried out. The oral, stomatognathic (temporomandibular joint), myofascial, and cervical screening examinations were noncontributory. The neurologic screening examination of cranial nerves II to XII was noted to be within normal limits, with the exception of a decreased reaction to pin prick by approximately 20% in the V3 (mandibular) distribution of the trigeminal nerve. This decreased reaction to pin prick was restricted to the mental nerve distribution bilaterally. An area of increased reactivity to light touch was noted in the left mental nerve distribution and along the right border of the lower lip. The treatment recommended was capsaicin (Zostrix) applied topically on the affected site, five times a day for 1 week, and three times a day thereafter. In addition, the patient was placed on a low dose of desipramine hydrochloride to enhance pain relief. At 6-month follow-up, the patient had no pain and continued

to use 10 mg of desipramine hydrochloride and capsaicin daily.

Case 3

A retired man, aged 67 years, presented with a bilateral continuous dull aching pain in the preauricular region. This pain extended to the inferior half of each ear. The patient also complained of continuous tenderness behind the upper half of the right ear. The condition had a sudden onset following face-lift surgery 18 months previously. A postoperative infection in the left preauricular area had complicated the surgery. No treatment had been provided for his continuing discomfort. Shaving in the affected areas elicited a burning, stinging sensation. Mastication or touching the side of his face also exacerbated his discomfort. The patient's sleep was disturbed because of the resultant discomfort from the pillow touching his face (hyperesthesia); nothing reportedly alleviated the pain. At the UCLA Pain Management Center, School of Dentistry, clinical findings revealed normal intraoral, stomatognathic (temporomandibular joint), myofascial, and cervical screening. Although an active trigger point was detected in the left masseter muscle, on palpation it failed to reproduce the patient's chief complaint. The cranial nerve screening examination identified a bilateral preauricular zone that was hypersensitive to both light touch and pin prick. The treatment recommended was to use capsaicin (Zostrix) cream in the affected areas five times a day for 1 week and then three times a day thereafter. Desipramine hydrochloride was prescribed to enhance both pain relief and sleep.

At 1-week follow-up, the burning quality had disappeared completely, and the patient's sleep had improved significantly. The maximum dose of desipramine hydrochloride was 30 mg. At 3-month follow-up, the patient no longer used the capsaicin because he had developed skin irritation in the region of application. In addition, the patient no longer used desipramine hydrochloride.

As part of an ongoing facial thermography study at the UCLA Medical Center, all three patients received investigational facial thermograms using an Agema 870 Thermovision unit (Secaus, NY) at 0.5°C and 1.0°C imaging sensitivity (0.1°C accuracy). All three patients displayed asymmetric lateral facial thermograms. Initially, the facial temperature (due to vascular heat emission) in the region of pain was increased, being asymmetric from side to side and rated as "hot" in the affected region. The pretreatment ΔT values (area temperature differences from side to side) ranged from +0.7°C to +1.1°C. Posttreatment thermograms, which were also obtained from all three patients, demonstrated decreased heat emission following cessation of the pain. In the affected regions of the face, ΔT values ranged from + 0.2°C to +0.4°C. All three patients had been instructed not to use capsaicin for 24 hours prior to their thermography examinations. Figure 1 is an example of a pretreatment lateral facial thermogram demonstrating a "hot" area (3 cm × 3 cm, yellow area with red ring) over the left cheek of the face. This area was measured and found to have increased vascular heat emission, judged as being "hot." Figure 2 is an example of a posttreatment lateral facial thermogram demonstrating a "warm" area (1 cm × 0.7 cm, yellow spot with red ring) over the same left cheek area of the face. This area was measured and found to have less increased vascular heat emission and was judged as being "warm." The thermographic examinations were comfortable for the patient and easy to perform, and all three patients enjoyed viewing their own thermal images.

Discussion

This presentation described three cases of traumatic neuralgia that responded to combinations of antidepressants and topical capsaicin. Although there was no control and a combined therapy was used, this combination is believed to be more effective for neuropathic orofacial pain than the use of either of these agents independently. Although many other therapies that may have been useful for this patient population exist, it is suggested that the first line of treatment include a tricyclic antidepressant in combination with topical capsaicin. If this treatment fails, it may be useful to consider membrane-stabilizing medications such as carbamazepine, baclofen, phenytoin, mexiletine, or even clonazepam. If the pain is localized intraorally, topical anesthetics may be delivered via a neurosensory shield (stent) in combination with oral medications.[26] Consideration must be given during the work-up to sympathetically maintained pain. Should the pain be eliminated by sympathetic block (stellate block), repeated blockade combined with antidepressants or membrane-stabilizing medications may be useful.

Often the question arises whether the antidepressants are effective secondary to their antidepressant properties, their effect on sleep, or through anal-

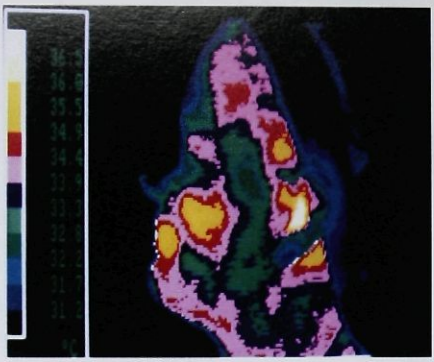

Fig 1 Pretreatment thermogram of subject 1. Note elevated temperature (yellow area with red ring) in mid-face area.

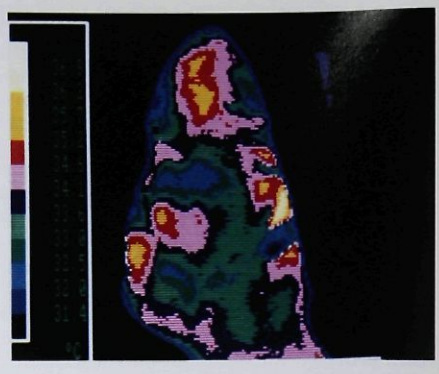

Fig 2 Posttreatment thermogram of subject 1. Note reduction of "hot" area (yellow area with red ring) in mid-face area.

gesic properties. It is generally accepted that the effect is independent of antidepressant effects; as lower doses are required, the time to onset is more rapid, and the majority of the pain patients are not depressed. Sleep is usually considered to be disturbed secondary to the pain, and in itself, may result in lowered pain threshold. There is no conclusive evidence that one antidepressant is superior to another. Therefore, clinical experience must be used to weigh the therapeutic benefits versus the patient's tolerance of side effects. A cautious review of the patient's previous and current medical history is required to identify conditions, such as arrhythmia and epilepsy, that contraindicate the use of tricyclics. Accommodation to some of the more bothersome side effects, such as dry mouth or sedation, can occur if the medication is prescribed initially in small incremental doses. Other side effects (eg, weight gain) may be unacceptable to the patient and require consideration of an alternative medication. Intolerance to side effects should not be confused with lack of efficacy of the medication, and under these conditions, a similar medication within the same group may be tried. When efficacy is truly in doubt, a medication from a different class of antidepressants should be prescribed. It is suggested that the first choice should be drugs that have low anticholinergic properties, such as desipramine hydrochloride or nortriptyline hydrochloride. Blood levels of these medications are also sometimes helpful in patients who are not responding to treatment. It has been observed that metabolism of the drug is variable and high doses may render a subtherapeutic level.

The initial application of capsaicin to skin causes C-fiber activation and pain; however, repeated application causes desensitization and hypalgesia. Despite the large amount of experimental work done with capsaicin, the exact mechanism of pain remains uncertain. Most studies have used capsaicin that was systematically applied to nerve trunks or directly injected into tissues. In the few studies that have used topically applied capsaicin, the concentrations were many times higher than those used clinically.[16] Several important issues associated with the use of capsaicin need to be clarified. Substance P is not selectively depleted by capsaicin. Marked reductions in the levels of a number of other peptides (including calcitonin gene-related peptide, somatostatin and vasoactive intestinal peptide) have also been found.[27] Rat studies have identified toxic and degenerative changes in neurons following exposure to capsaicin.[28,29] If capsaicin does reduce substance P levels by causing C-fiber degeneration, the long-term effect of this, in humans, needs to be evaluated. Capsaicin application on neurons has diffuse effects, and its pain-relieving effects are unlikely to be solely because of reduction of substance P levels. Until the exact mechanism of capsaicin is understood, clinicians should give careful consideration to its long-term use. However, the significant pain reduction resulting from the topical application of capsaicin, in certain types of

neurogenically mediated pain conditions, warrants the continued clinical study of capsaicin as an analgesic/pain-modulating substance.

References

1. Casey KL. Toward a rationale for the treatment of painful neuropathies. In: Dubner R, Gebhart GF, Bond MR (eds). Proceedings of the Vth World Congress on Pain. Amsterdam: Elsevier Science Publishers BV, 1988: 165–174.
2. Dorland's Pocket Medical Dictionary. Philadelphia, Saunders.
3. Fields HL. Painful dysfunction of the nervous system. In: Fields HL (ed). Pain. New York: McGraw-Hill, 1987:134–137.
4. Janig W. Pathophysiology of nerve following mechanical injury. In: Dubner R, Gebhart GF, Bond MR (eds). Proceedings of the Vth World Congress on Pain. Amsterdam: Elsevier Science Publishers BV, 1988:89–108.
5. Dyck PJ, Lambert EH, O'Brien PC. Pain in peripheral neuropathy related to rate and kind of fiber degeneration. Neurology 1976;26:466–471.
6. Wall PD. Mechanism of acute and chronic pain. In: Kruger L, Liebeskind JC (eds). Advances in Pain Research and Therapy, vol 6. New York: Raven Press, 1984:95–104.
7. Wall PD. Pain and no pain. In: Coen CW (ed.). Functions of the Brain. Oxford: Clarendon Press, 1985:44–66.
8. Otsuka M, Konishi S, Yanagisawa M, Tsunoo A, Takagi H. Role of substance P as a sensory transmitter in spinal cord and sympathetic ganglia. Ciba Found Symp 1982; 91:13–34.
9. Lotz M, Carson DA, Vaughan JH. Substance P activation of rheumatoid synoviocytes: Neural pathway in pathogenesis of arthritis. Science 1987;235:893–895.
10. Levine JD, Clark R, Devor M, et al. Intraneuronal substance P contributes to the severity of experimental arthritis. Science 1984;226:547–549.
11. Badalamente MA, Cherney SB. Periosteal and vascular innervation of the human patella in degenerative joint disease. Semin Arthritis Rheum 1989;18:61–66.
12. Levine JD, Goetzl EJ, Basbaum AI. Contribution of the nervous system to the pathophysiology of rheumatoid arthritis and other polyarthritides. Rheum Dis Clin North Am 1987;13:369–383.
13. Colpaert FC. Evidence that adjuvant arthritis in the rat is associated with chronic pain. Pain 1987;28:1277–1289.
14. Lam FY, Ferrell WR. Capsaicin suppresses substance P-induced joint inflammation in the rat. Neurosci Lett 1989; 105:155–158.
15. Virus RM, Gebhart GF. Pharmacologic actions of capsaicin: Apparent involvement of substance P and serotonin. Life Sci 1979;25:1273–1284.
16. Lynn B. Capsaicin: Actions on nociceptive C-fibres and therapeutic potential. Pain 1990;41:61–69.
17. Dini D, Bertelli G, Gozza A, Forno GG. Treatment of the postmastectomy pain syndrome with topical capsaicin. Pain 1993;54:223–226.
18. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. J Am Acad Dermatol 1989;17:265–270
19. Sicuteri F, Fusco B, Marabini S, Fanciullacci M. Capsaicin as a potential medication for cluster headache. Med Sci Res 1988;16:1079–1080.
20. Ross DR, Varipapa RJ. Treatment of painful diabetic neuropathy with topical capsaicin. N Engl J Med 1989;321: 474–475.
21. Raynor HC, Atkins RL, Westerman RA. Relief of local stump pain by capsaicin cream. Lancet 1989;2:1276–1277.
22. Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. Oral Surg Oral Med Oral Pathol 1990;69:287–290.
23. Gregg JM. Studies of traumatic neuralgias in the maxillofacial region: Surgical pathology and neural mechanisms. J Oral Maxillofac Surg 1990;48:228–237.
24. Meyer RA. Discussion on Gregg JM. Studies of traumatic neuralgias in the maxillofacial region: Symptom complexes and response to microsurgery. J Oral Maxillofac Surg 1990;48:141.
25. Bashi N. Preventing and resolving complications with osseointegrated implants. Dent Clin North Am 1989; 33(4):821–868.
26. Graff-Radford SB. Differential diagnosis of orofacial pain. In: Hardin JF (ed). Clark's Clinical Dentistry. Philadelphia: Lippincott JB, 1993:1–15.
27. Holzer, P. Local effector functions of capsaicin sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. Neurosci 1988;24:739–768.
28. Jancso G, Kiraly E, Joo F, Such G, Nagy A. Selective degeneration by capsaicin of a sub population of primary sensory neurons on the adult rat. Neurosci Lett 1985;59: 209–214.
29. Marsh SJ, Stansfeld CE, Brown DA, Davey R, McCarthy D. The mechanism of action of capsaicin on sensory C-type neurons and their axons in vitro. Neurosci 1987;23:275–289.

Resumen

Disestesia traumática del nervio trigémino

Las lesiones traumáticas de los nervios periféricos a menudo traen como consecuencia una molestia persistente. Se ha implicado que la substancia P es un mediador del dolor, y cuando este neurotransmisor disminuye, se produce una reducción del dolor. En este estudio, personas que sufrían de disestesia traumática del nervio trigémino fueron tratadas con capsaicina, la cual reduce la presencia de la substancia P, con efectos a largo plazo. Este tipo de terapia puede ser utilizada individualmente o en combinación con otras intervenciones farmacológicas en el tratamiento de la disestesia traumática del nervio trigémino.

Zusammenfassung

Traumatische Dysästhesie des N. trigeminus

Traumatische Verletzungen der peripheren Nerven resultieren oft in bleibenden Beschwerden. Substanz P ist als Schmerzvermittler damit in Zusammenhang gebracht worden. Die Erschöpfung dieses Neurotransmitters hat eine Schmerzreduktion zur Folge. Personen, welche an einer traumatischen Dysästhesie des N. trigeminus leiden, wurden mit Capsaicin behandelt, welches über längere Zeit zur Erschöpfung der Substanz P führt. Diese Form der Therapie kann individuell oder in Kombination mit anderen pharmakologischen Interventionen bei der Behandlung von traumatischer Dysästhesie des N. trigeminus verwendet werden.