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Neuropathic Pain Can Be Relieved by Drugs That Are Use-dependent Sodium Channel Blockers: Lidocaine, Carbamazepine, and Mexiletine

DARRELL L. TANELIAN, M.D., PH.D.,* WILLIAM G. BROSE, M.D.†

Pain due to acute or chronic nerve injury is difficult to treat and is often resistant to conventional analgesics.^{1,2} Common pain syndromes attributed to peripheral nerve injury include posttraumatic neuralgia, diabetic peripheral neuropathy, postherpetic neuralgia, phantom limb pain, ischemic neuropathy, and postirradiation neuropathy.³⁻⁷ The use of agents known to block sodium channels in a use-dependent fashion (lidocaine, mexiletine, and carbamazepine) is a relatively new therapeutic intervention that is achieving success in the management of neuropathic pain.^{1-2,8-11} We report four cases of chronic neuropathic pain that were responsive to the use-dependent sodium channel blockers, lidocaine, mexiletine, and carbamazepine.

CASE REPORTS

Case 1. The patient was a 72-yr-old woman with a 2-yr history of left lower extremity phantom limb pain following amputation below the knee secondary to diabetes. The patient reported four types of pain contributing to an overall constant pain level of 8-9 of 10 on a

visual analog scale (VAS). She described her pain as originating in the nonexistent left lower leg and characterized the sensations as: a sharp, "cutting" pain lasting about 1 min each day; an ice-cold sensation; numbness over her missing left foot and toes; and a constant electric shock sensation over the entire missing lower limb. Nonsteroidal antiinflammatory drugs (NSAIDs), Elavil, and Vicodin (hydrocodone 50 mg/day) did not improve the pain or abnormal sensations. The patient received carbamazepine (100 mg orally every hour) and was instructed to increase the dose by 100 mg every 3 days until pain control was achieved (maximum of 1,200 mg/day). Upon returning to the pain clinic 1 week later, taking 100 mg carbamazepine orally three times per day, the patient reported significant pain relief, such that the VAS was now 2-3 of 10. The patient continues to receive this dose of carbamazepine and has continued to have good pain control for the past 11 months.

Case 2. A 74-yr-old woman with a 5-yr history of metastatic breast carcinoma developed severe left hand and arm pain 6 weeks prior to presenting to the pain clinic. As part of her therapy she had received irradiation to her left supraclavicular and axillary region 18 months previously. A magnetic resonance imaging (MRI) scan of her left neck, axilla, and arm revealed no evidence neither of tumor nor of abnormality of the left arm innervation. Physical examination revealed an edematous left arm and hand. There was total absence of motor function in all muscle groups of the patient's left hand, as well as 2/5 motor strength of the upper arm musculature. The patient described chronic unremitting pain of her left arm and hand, characterized as tingling, burning, and intermittently sharp pain, especially with movement. Sensory examination revealed a loss of sensation of vibration, light touch, and cold in the left hand. The skin on the forearm region was hypersensitive to stroking. Aspirin, acetaminophen, ibuprofen, and codeine (300 mg/day) had all failed to control the pain. Pain therapy with carbamazepine was started at 100 mg orally every hour, and at a dosage of 200 mg orally three times per day (serum concentration 7.1

* Assistant Professor of Anesthesia.

† Assistant Professor of Anesthesia.

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Address reprint requests to Dr. Tanelian: Department of Anesthesia, Room S-268, Stanford University School of Medicine, Stanford, California 94305.

$\mu\text{g/ml}$), the patient reported a reduction in her pain from 8 to 3 on a 10-cm VAS. The mechanical hypersensitivity of the forearm was alleviated as well. Nine months later the patient continues to have good pain control.

Case 3. A 64-yr-old man presented with bilateral foot and leg pain of 7 yr duration. He described his pain as a constant burning sensation most intense in the soles of his feet and extending circumferentially over the legs. Electromyograms performed on initial presentation showed evidence of partial denervation; nerve conduction velocities were uniformly subnormal. The overall picture was that of a sensorimotor polyneuropathy. Pain management at the time of initial evaluation had consisted of short-acting opiates combined with benzodiazepines. Previous trials of tricyclic antidepressants and NSAIDs were unsuccessful. The patient received a trial of intravenous lidocaine (5 mg/kg in 20 ml normal saline), which decreased his pain from 7 to 1 on a 10-cm VAS. Two hours after the lidocaine infusion was discontinued, the patient's pain returned to a level of 7 of 10. A normal saline infusion (20 ml) was then administered, and the patient's pain level was unaltered by this intervention. Subsequently, treatment with oral mexiletine was initiated at 450 mg/day, and the dose increased until pain control was achieved. After 1 week of mexiletine therapy, the patient reported complete resolution of his burning pain while receiving a dose of 900 mg/day. The patient continues to experience pain relief after 1 yr.

Case 4. A 67-yr-old woman presented to the pain clinic with complaints of total body burning pain of 18 months' duration. The patient had a history of metastatic breast carcinoma initially treated with surgical excision and chemotherapy. The pain complaints started with burning pain of stocking-and-glove distribution that developed during the course of *cis*-platinum therapy. The pain became more generalized and severe throughout the next several months. Oral opioids in increasing doses and tricyclic antidepressants had been unsuccessful in managing her pain. At the time of initial consultation, the patient was hospitalized and obtunded while receiving oral morphine (480 mg orally per day) and hydromorphone (40 mg orally per day) combined with lorazepam. Intravenous lidocaine was initiated at 70 mg/h. Opioid and benzodiazepine therapies were discontinued. Within 24 h of the new therapeutic regimen the patient was analgesic and well-oriented. Several hours after discontinuation of the lidocaine the patient reported pain at a level of 8 of 10 on the VAS. Infusion of normal saline did not improve the patient's pain. Reinstitution of the lidocaine infusion at 70 mg/h decreased the pain to a level of 2 of 10. Gradual institution of oral mexiletine starting at 200 mg orally once per day allowed for discontinuation of the lidocaine. The patient was discharged from the hospital with good analgesia (VAS score 2 of 10) on oral mexiletine therapy alone (800 mg/day). Two months later, tumor progression required the addition of oral methadone (10 mg/day). This combination of mexiletine and methadone continue to provide pain control for the past 13 months.

DISCUSSION

Damage to peripheral nerves, especially those involved in the appreciation of pain (A-delta and C fibers), can lead to acute and chronic pain.³⁻⁷ Normally, a strong mechanical, thermal, or chemical stimulus is required to activate these pain fibers (nociceptors). However, when these nerves are damaged by injury or other pathologic conditions, they may chronically produce nerve impulses in the absence of any noxious stimulus. This condition is known as "pathophysiologic" or "neuropathic" pain. The spontaneous generation of neural activity in A-delta and

C fiber nerve terminals in conditions of neuropathic pain has been documented using microneurography in animals and humans.¹²⁻¹⁷

The most common conditions associated with neuropathic pain are: posttraumatic neuromas, postamputation (phantom limb) pain, diabetic neuropathy, postherpetic neuralgia, ischemic neuropathy, nutritional neuropathy, alcoholic neuropathy, and postirradiation neuropathy. Clinically, these patients present with complaints of spontaneous pain, hyperalgesia, hyperpathia, and allodynia.³⁻⁷ Pain usually is experienced in the extremities and is described as a superficial burning, deep aching, or stinging pain. In addition, paroxysmal, lancinating, electric shock-like pain radiating through a limb has been reported.^{6,7} In some conditions, hyperesthesia and hyperpathia may be the predominant complaint.⁵

The etiology and pathology of these pain syndromes are not fully known. Nerve conduction studies generally disclose abnormalities of mainly the small myelinated (A-delta) and unmyelinated C fibers.³⁻⁷ Demyelination of nerves predominates over axonal degeneration.³ In addition, changes can occur at the level of the spinal cord.¹⁸

Electrophysiologically, agents that block sodium channels are able to suppress spontaneous injury and neuroma discharge in A-delta and C fibers.^{17,19} The ability of sodium channel blockers to be frequency- and voltage-dependent in their action is essential for their clinical utility.¹⁹⁻²¹ Because of these properties, sodium channel blockers are able to target spontaneously active nerves while not effecting conduction in normal nerves. Agents known to produce frequency-dependent sodium channel blockade as well as relieve pain include lidocaine,^{2,8,9,11} carbamazepine,¹ and mexiletine.¹⁰

The treatment of neuropathic pain is difficult, but it appears to be responsive to use-dependent sodium channel blockers. We have found that lidocaine given intravenously can be effective as a diagnostic agent to identify whether a patient's pain is responsive to this type of therapy. Intravenous lidocaine has been shown to predict the efficacy of oral mexiletine to control cardiac arrhythmias.²² Oral therapy for neuropathic pain can be instituted with carbamazepine or mexiletine. Further, prospective double-blind studies are needed to establish the efficacy of this therapy and to identify the conditions that are most responsive to these agents.

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