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Levorphanol for Treatment of Intractable Neuropathic Pain in Cancer Patients

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Abstract

Neuropathic pain in cancer patients is often difficult to treat, requiring a combination of several different pharmacological therapies. We describe two patients with complex neuropathic pain syndromes in the form of phantom limb pain and Brown-Sequard syndrome who did not respond to conventional treatments but responded dramatically to the addition of levorphanol. Levorphanol is a synthetic strong opioid that is a potent N-methyl-D-aspartate receptor antagonist, mu, kappa, and delta opioid receptor agonist, and reuptake inhibitor of serotonin and norepinephrine. It bypasses hepatic first-pass metabolism and thereby not subjected to numerous drug interactions. Levorphanol's unique profile makes it a potentially attractive opioid in cancer pain management.

Keywords: Brown-Sequard syndrome; cancer; cancer pain; levorphanol; neuropathic pain; phantom limb pain

Introduction

One-third of cancer patients who experience pain also experience neuropathic pain[1] and about half the patients with cancer who suffer from neuropathic pain also have nociceptive pain.[2] Most neuropathic pain exists as mixed pain in combination with nociceptive pain. Treatment of neuropathic pain is often challenging. Several drugs such as gabapentinoids, duloxetine, amitriptyline, opioids, and topical agents have been studied with mixed results.[3,4] Guidelines and findings of studies involving noncancer neuropathic pain syndromes are often extrapolated into treatment of neuropathic pain in cancer patients.[4] Cancer-related neuropathic pain may be chemotherapy related, radicular pain from tumor involvement, postsurgical neuropathic pain, postherpetic neuralgia, and other kinds of neuropathic pain.[4–7] Neuropathic pain in cancer patients may also exist as rare conditions such as phantom limb pain (PLP) and Brown-Sequard syndrome (BSS).

PLP is defined as a painful sensation originating in the amputated limb that usually develops within days after amputation.[8] It is estimated that 50% of people with limb amputations develop PLP.[8] It is usually described as shooting, shocking, burning, tingling, aching, and pins and needles-like sensation in the absent limb.[8] Peripheral nerve ending changes, structural reorganization of spinal cord and primary somatosensory cortex, and increased sensitization of spinal cord may be the neurological basis for PLP.[8,9] Because the pathophysiology of PLP is not clearly understood, the treatment options are mainly based on clinical experience.[9] There are case series showing that tramadol and methadone may be helpful. Antidepressants, antiepileptics, ketamine, calcitonin, memantine, spinal cord stimulator, ablation of spinal cord dorsal root, anterolateral cordotomy, and sympathectomy, have shown mixed results.[9,10] Treatments such as transcutaneous electrical nerve stimulation and mirror therapy have shown modest benefit.[8–10]

BSS like PLP is a difficult to treat cause of neuropathic pain. BSS refers to an injury of the spinal cord where one side is damaged more than the other, resulting in ipsilateral weakness and position sense loss, but with contralateral pain and temperature sensation loss below the affected level of spinal cord.[11] This is because motor fibers of the corticospinal tracts cross at the junction of the medulla and spinal cord and ascending dorsal column (vibration and position sensation) crosses above the spinal cord in the medulla. Whereas the spinothalamic tract carries pain, temperature, crude touch sensations from the contralateral side of the body.[12] BSS can be caused by both traumatic and nontraumatic causes.[12,13] BSS has also been reported as a delayed complication of

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stereotactic body radiotherapy in cancer patients.[14,15] Along with physical therapy, several treatment regimens are proposed with only modest efficacy for BSS such as high-dose steroids, hyperbaric oxygen, pentoxyphylline, anticoagulation, vitamin E, and bevacizumab.[11,13–18]

We present two patients with PLP and BSS who did not respond to conventional treatments but demonstrated major improvement after the addition of levorphanol.

Case Description

Patient 1

A woman in her 30s was diagnosed with osteosarcoma involving the right-sided proximal humerus with metastasis to the scapula. She underwent radical resection of the right proximal humerus with reconstruction. During the postoperative period, morphine was ineffective and was later switched to hydromorphone. Unfortunately, she developed recurrent disease in the right axilla, shoulder, chest wall, and upper arm. She complained of constant ''achy'' pain (intensity of 8 out of 10 on the Edmonton Symptom Assessment System [ESAS][19] pain score) in the right shoulder with radiation down the arm. At times, she also described combination of burning with pins and needle sensation. Tramadol 50 mg tablets four times a day and later hydromorphone 2 mg tablets six times a day were ineffective for her pain, leading to the initiation of hydromorphone extended-release 16 mg once daily with hydromorphone immediate release 4 mg tablets prescribed for breakthrough pain every four hours as needed. Gabapentin 300 mg once daily at bedtime was also initiated. This regimen controlled her pain (intensity of 3 out of 10 ESAS pain score).

Further progression in disease led to right-sided forequarter amputation. During the postoperative period, her pain was initially well managed with intravenous hydromorphone infusion and changed to home regimen of oral hydromorphone extended-release. Shortly afterward, she developed worsening in her pain. The achy pain in the area of the right upper extremity was now replaced by constant ''tingling and shooting pain'' sensation (7 out of 10 ESAS pain score) at the site of amputated limb, causing her significant distress. She was diagnosed with PLP. During this time, the combination of hydromorphone extended-release 16 mg once daily, hydromorphone 4 mg six times a day, and gabapentin 300 mg three times a day was ineffective. A trial of increase in gabapentin resulted in drowsiness, prompting a decrease back to previous dose. An opioid rotation to methadone was not pursued due to potential interaction with an antineoplastic agent. Levorphanol was initiated at 2 mg every eight hours scheduled with hydromorphone 4 mg every four hours as needed for breakthrough pain. A week later, she reported the PLP had almost completely resolved (intensity of 0–1 out of 10 ESAS pain score). She reported no side effects. For the next several months, the patient continued to report excellent control of the PLP. She ran out of levorphanol for a period of three days, which resulted in the recurrence of severe PLP. Despite taking hydromorphone 4 mg every four hours around-the-clock and continuing gabapentin, she remained with uncontrolled pain until she was restarted on levorphanol. At that point her ESAS pain intensity returned back to previous levels of 0–1 out of 10.

Patient 2

A woman in her 40s was diagnosed with metastatic right-sided breast cancer to lymph nodes and thoracic vertebra. She underwent chemotherapy, right-sided modified radical mastectomy, axillary lymph node dissection, postmastectomy radiation to the right-sided chest wall, and stereotactic radiation to the metastatic disease on the thoracic vertebral body. Approximately one year later, she began to experience a burning sensation over the mid back area. Magnetic resonance imaging of the spine revealed a syrinx and myelomalacia with enhancement and enlargement of the cord centrally and to the left at the site of the radiation. Shortly afterward, she developed weakness in the left leg associated with loss of balance and foot drop along with tingling, burning, and numbness in her right lower extremity. She developed abnormal sensation to sharp stimulus, light touch, or vibration in the right lower extremity. She was diagnosed with BSS. High-dose dexamethasone was prescribed without any benefit. She continued to have severe neuropathy in the right lower extremity and progressive weakness prompting intensification in her physical therapy. Although the burning sensation over the mid back resolved, the severe neuropathic pain in her right lower extremity (5–10 out of 10 on the ESAS pain item) was intractable to tramadol, hydrocodone, hydromorphone, methadone, pregabalin, gabapentin, duloxetine, venlafaxine, nortriptyline, amitriptyline, and other drugs such as accutane, pentoxifylline, and supplementation with high-dose B and E vitamins. She was on 1200 mg of gabapentin three times a day, venlafaxine extended-release 75 mg once daily, and hydrocodone/acetaminophen 10/325 mg taken every six hours scheduled and still complained of uncontrolled pain. She was started on a low dose of levorphanol at 1 mg taken every eight hours scheduled with continuation of hydrocodone/acetaminophen 10/325 mg taken as needed. At one-month follow-up, she experienced drastic improvement in her pain, burning, and tingling sensation (2 out of 10 on the ESAS pain item). This improvement persisted at subsequent follow-ups for the next several months. She rarely required the use of any hydrocodone and was later discontinued. She continued to use gabapentin and venlafaxine.

Discussion

Despite recent advances in cancer pain management, neuropathic pain remains one of the most challenging symptoms to treat.[4,20–24]Neuropathic pain often is a predictor of poor overall response to opioid analgesics in cancer patients.[22,23,25–27] Our team used levorphanol, a rarely prescribed opioid to successfully treat intractable neuropathic pain syndromes in the form of PLP and BSS in two patients.

Levorphanol, a synthetic strong opioid, was approved in the United States in the 1950s. It is an agonist at the mu, kappa, and delta opioid receptors, reportedly more potent than methadone. It is a very potent N-Methyl-D-aspartate receptor antagonist, more so than methadone and perhaps even ketamine.[28,29] It is also a reuptake inhibitor of both serotonin and norepinephrine (perhaps weaker than methadone).[28,30–32] It has no known cardiac corrected QT (QTc) prolongation effects.[28] It bypasses first-pass metabolism in the liver by the cytochrome P450 enzymes and hence subjected to negligible drug interactions as compared with methadone.[30]

Levorphanol undergoes glucoronidation through UDP-glucuronosyltransferase to levorphanol-3-glucoronide, which is renally excreted. Owing to its unique profile, it may be an attractive drug to treat complex pain syndromes, opioid-induced hyperalgesia, neuropathic pain, and refractory pain syndromes.[28,30–36] Side effects for levorphanol are similar to those of other opioids. It has a shorter half-life than methadone (11–16 hours vs. 8–60 hours),[30,31,34,37] and accumulates at a slower pace reaching a steady state in approximately three days. It appears to have a safer profile than methadone and yet possesses the desirable unique properties of methadone.[31,38,39]

The accurate opioid rotation ratio (ORR) from other opioids to levorphanol is unknown. It is estimated that levorphanol is approximately six to eight times more potent than morphine.[32,34] Our two patients had an ORR from morphine equivalent daily dose (MEDD) to levorphanol of 13.3 and 20. Patient 1's MEDD was 80 mg (16 mg hydromorphone × 5) and was rotated to 6 mg of levorphanol/day with an ORR of 13.3 (MEDD/levorphanol mg = 80/6 = 13.3). Similarly, patient 2's MEDD was 60 mg (40 mg hydrocodone × 1.5) and was rotated to 3 mg of levorphanol/day with an ORR of 20 (MEDD/levorphanol mg = 60/3 = 20). Studies investigating the ORR of other opioids to levorphanol are clearly required to safely and efficiently conduct opioid rotations.

Limited data exist regarding the efficacy of levorphanol in cancer pain management. In adults with chronic neuropathic pain, higher doses of levorphanol (average 9 mg/day) were more effective than lower doses of levorphanol (2.7 mg/day) in reducing the intensity of neuropathic pain.[35] Seventy-four percent (23/31) of patients with chronic nonmalignant pain who did not respond to other opioids and adjuvants including methadone responded to levorphanol.[34] There are case reports of its efficacy in intractable nociceptive cancer pain.[33] Well-designed randomized controlled trials are needed to study the effect of levorphanol on cancer-related nociceptive, neuropathic, and mixed pain syndromes, along with unique scenarios such as PLP and BSS. Our two patients were fortunate that levorphanol was covered by their health insurance plan and available in their local pharmacy. Unfortunately, levorphanol is not readily available in most pharmacies and may require a significant period of time to enable the pharmacy to place an order and acquire the drug before dispensing to the patient. Proactive planning by both the prescriber and the patient is hence required to ensure there are no interruptions in drug use. Moreover, regional differences in availability of levorphanol may exist. In addition to drug availability issues, the lack of training and familiarity with levorphanol, limited data on its use in cancer patients, and availability of cheaper and newer opioids make levorphanol a ''forgotten opioid.''[37] The dramatic improvement in neuropathic pain after the addition of levorphanol in our two patients calls for more research and revival of this opioid in cancer pain management.

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Author Disclosure Statement

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