Case Report

Successful reduction of neuropathic pain associated with spinal cord injury via of a combination of intrathecal hydromorphone and ziconotide: a case report

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Study design: Case report.

Objectives: To report a novel management strategy for neuropathic pain management after spinal cord injury.

Setting: Outpatient spinal cord injury (SCI) clinic.

Methods: The patient demonstrated two neuropathic pain syndromes, namely at- and below-level pain. These syndromes were recalcitrant to conservative measures and a decision was made to proceed with intrathecal therapies.

Results: The patient's at-level pain was responsive to intrathecal hydromorphone but the below-level pain was unaffected by this intervention. Intrathecal ziconotide provided an opposite response with a positive effect observed on the below-level pain and minimal effect on the at-level pain. The combination of intrathecal ziconotide and hydromorphone provided effective relief for both components of the patient's SCI associated neuropathic pain.

Conclusions: The combination of intrathecal ziconotide and hydromorphone has the potential to provide significant pain relief for patients with neuropathic pain associated with spinal cord injury.

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Introduction

Pain following traumatic spinal cord injury (SCI) is a common clinical problem that can afflict patients for decades after their initial injury. SCI pain can result from various etiologies including neuropathic, somatic and visceral.¹ SCI-associated neuropathic pain can be classified by location into three categories, namely above, at and below the level of the spinal lesion, respectively.² Although various treatment strategies have been purported as efficacious in SCI-associated neuropathic pain, this entity can be notoriously challenging to treat.³

Intrathecal delivery of medications is a well-recognized technique for the management of severe spasticity and chronic pain. Although several agents are commonly used clinically,^{4,5} only three agents currently have FDA approval for use. Baclofen, a GABA-B agonist, is the mainstay of intrathecal therapy for spasticity and is FDA approved for this indication. Morphine, considered by many clinicians to be the first-line agent for

intrathecal pain management, is approved for use in chronic severe pain. This agent has been used clinically for over two decades. Intraspinal opiates, such as morphine and hydromorphone, are thought to exert their therapeutic effect by inhibition of a subset of presynaptic N-type voltage-sensitive calcium channels and the activation of postsynaptic potassium channels.⁶ Ziconotide, a 25 amino-acid peptide, was approved for use in the United States in 2004 for chronic severe pain. This agent is only effective via intrathecal delivery and is thought to exert its anti-nociceptive properties by binding to and directly blocking voltage-sensitive calcium channels without interfacing with opioid receptors.⁷ This medication has demonstrated effectiveness in refractory pain conditions,⁸ including in AIDS and cancer.⁹ A recently published clinical trial of ziconotide included a very high percentage of neuropathic pain patients. Ziconotide has a number of potential advantages over the intraspinal opiates. Perhaps the most significant benefits of this agent are that there is no associated respiratory depression or withdrawal syndrome associated with the use of this medication. Although intrathecal ziconotide has poten-

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tial adverse effects, the clinical experience with this medication suggests that ziconotide infusion can be rapidly diminished for resolution of untold effects. The most commonly reported adverse events associated with ziconotide during clinical trials were dizziness, confusion, memory impairment, ataxia, abnormal gait, somnolence, headache, nausea, diarrhea and vomiting. The only laboratory abnormality that has been consistently associated with a ziconotide usage is CPK elevation. The use of multiple agents for intrathecal delivery is commonplace as using a combination of drugs with different mechanisms of action could potentially produce a synergistic anti-nociceptive effect.

Although acceptable stability of intrathecal opiates with other agents has been reported,¹⁰ there are stability concerns with utilization of ziconotide in combination with other agents. Shields *et al*¹¹ reported on the degradation of ziconotide in the presence of two opiate solutions. Ziconotide was more unstable in the presence of morphine compared to hydromorphone. The time for ziconotide at 25 mcg/ml to degrade by 20% stability was only 15 days in the presence of a morphine solution at 25 mg/ml. Ziconotide retained at least 80% stability for 40 days in the presence of hydromorphone at 35 mcg/ml compared to 15 days. Morphine and hydromorphone did not degrade significantly by the presence of ziconotide. Thus, utilization of ziconotide with these opiates presents a unique clinical challenge. The purpose of this case report is to present the effective use of intrathecal ziconotide and hydromorphone in combination for a neuropathic pain syndrome following traumatic myelopathy.

Case report

The patient is a 23-year-old white female who incurred a SCI following a fall from a two-storeyed building. She incurred a compression fracture of the fourth thoracic vertebrae. Her initial neurologic status was T5 ASIA A paraplegia. She required no orthopedic stabilization of her vertebral column. She had resultant neurogenic bowel and bladder but did not have significant hypertonicity. Bladder management required utilization of intermittent catheterization every 6 h. The patient's past medical history was significant for allergic rhinitis and hypothyroidism.

The patient reported two discrete pain syndromes: (1) constant, band-like, stinging pain across the chest, subsequently referred to as her at-level pain and (2) paroxysms of shooting, electrical-like pain in the thighs, calves and groin, subsequently referred to as her below-level pain. The patient recalls the presence of these pain complaints within 1 week of her spinal cord injury. She was 14 years post-injury at the time of presentation. The patient reported no specific or exacerbating factors to her pain. The patient did not demonstrate any evoked symptoms such as allodynia or hyperalgesia. The patient reported that the quality of pain symptoms had changed little from the time of her injury. Prior treatments for pain that were generally unsuccessful included tricyclic

antidepressants (amitriptyline and nortriptyline), anti-convulsants (phenytoin, tegretol and gabapentin), bio-feedback, hypnosis and spinal cord stimulation.

At the time of presentation, the patient was utilizing between 300 and 400 mg of oxycodone daily (using a combination of long-acting OxyContin and short-acting OxyIR). The patient reported that this medication was partially effective for her at-level pain and was ineffective for her below-level pain. One assessment tool that was utilized for this patient was the visual analogue scale of pain intensity (VASPI). In this method, patients are presented a 100 mm line with one end of the line referenced as 'no pain' and the other end of the line 'worse pain imaginable'. At initial assessment, the patient's VASPI was 89 for the combination of both pain syndromes.

Given the patient's partial response to oral oxycodone, a trial of intrathecal morphine was undertaken. The patient's oxycodone dose was weaned to 200 mg/day before the intrathecal morphine trial. A temporary intrathecal catheter was placed via a lumbar puncture. The thecal sac was entered at the L4–L5 interspace with the catheter being advanced superiorly to the T7 spinal level. A continuous infusion of preservative-free morphine commenced at 1 mg/day (41.7 mcg/h) without a loading bolus dose. Within 8 h of the initiation of the infusion, the patient developed diffuse pins and needles throughout her chest, back, legs and perineum. A diagnosis of intrathecal morphine-induced hyperalgesia¹² was made and the trial was discontinued. The new pain complaints ceased within 4 h after removal of the intrathecal catheter. The patient then resumed her oral pain regimen.

A second intrathecal trial with hydromorphone was undertaken 1 month after the initial trial. The weaning of oral medication and intrathecal catheter placement was similar to the initial trial. A continuous infusion of preservative-free hydromorphone was commenced at 200 mcg/day (8.3 mcg/h) without a loading bolus dose. The patient's intrathecal hydromorphone dosing was titrated every 12 h for 96 h up to a level of 1100 mcg/day (45.8 mcg/h). Over the course of the next 3 days, the patient reported partial pain relief from her at-level pain and minimal effect on her below-level pain. At this dosing, the patient reported a VASPI for her at-level pain as 42 and a VASPI for her below-level pain as 75. The trial was discontinued and a decision was made to proceed with implantation of a permanent intrathecal delivery system. Other than some transient constipation and nausea, the patient had no adverse effects from this intrathecal trial.

The patient underwent implantation of the intrathecal delivery system in the routine fashion.¹³ The initial starting of hydromorphone was 500 mcg/day (20.8 mcg/h). Over the next 15 months, the patient intrathecal hydromorphone was gradually titrated up to 8.5 mg/day (354 mcg/h). The patient found that the best relief was obtained with 8.5 mg of hydromorphone per day in combination with 400 mcg of baclofen per day. Baclofen was utilized for its adjuvant analgesic properties and not

for its antispasticity effects. This approach resulted in excellent relief of the at-level pain with a VASPI of 7 for this pain complaint but minimal effect on the below-level pain with a VASPI of 82 for this complaint. This pattern continued despite the addition of clonidine and bupivacaine to the hydromorphone/baclofen mixture. The patient continued to use short-acting oxycodone as a breakthrough agent, typically using between 75 and 90 mg of oxycodone per day.

Given the persistence of the patient's below-level pain syndrome, the patient was willing to embark on a trial of intrathecal ziconotide. The patient was weaned from her intrathecal mixture over the course of 30 days. Preservative-free saline was placed in the pump to maintain catheter patency with a flow rate of $0.2\text{ cm}^3/\text{day}$. She continued on an intrathecal saline infusion for 10 days before the initiation of intrathecal ziconotide. The patient was allowed to liberally increase her oxycodone dosing during the weaning from her intrathecal opiates. Her opiate consumption increased to 420 mg of oxycodone per day (again using a combination of OxyContin and OxyIR). The patient experienced bifrontal headaches during this weaning period. These headaches were relieved with oxycodone and were thus considered to be associated with intrathecal opiate withdrawal. Before proceeding with intrathecal ziconotide, the patient reported a VASPI of 78 for her at-level pain and 80 for her below-level pain.

The patient then proceeded with a trial of intrathecal ziconotide. Her initial starting dose was 2.4 mcg/day. This medication was titrated every 12–14 days in increments of 0.5–0.6 mcg/day. Over the course of 6 months, the patient eventually achieved intrathecal ziconotide dosing of 10 mcg/day. The patient again was allowed to adjust her oral medication according to her pain level. Her total oxycodone use decreased to between 200 and 250 mg/day. This approach resulted in positive effects on the patient's below-level pain, VASPI = 4, while having minimal effects on the patient's at-level pain component, VASPI = 72. With the commencement of intrathecal ziconotide use, the patient had to increase the frequency of intermittent catheterization to 5–6 times per day. The patient's urodynamic findings did not change significantly. The patient's laboratory findings, including creatinine kinase, did not change significantly. Otherwise, the patient had no adverse effects from intrathecal ziconotide.

Given the alternative responsiveness of the intrathecal opiates and ziconotide to the various components of the patient's SCI-related pain, a decision was made to attempt to utilize intrathecal hydromorphone and ziconotide in combination. As ziconotide stability is affected by the presence of hydromorphone, the intrathecal ziconotide dosing was increased to 11 mcg/day. The ziconotide concentration remained stable at 25 mcg/ml as increasing concentrations of hydromorphone were added to the intrathecal mixture. The initial hydromorphone concentration was 1 mg/ml, which resulted in an intrathecal hydromorphone dosing of 0.44 mcg/day. The patient returned monthly for dosing

Figure 1 Patients VASPI scores during treatment

adjustments and pump refills. The hydromorphone concentration was adjusted in increments of 0.5 mg/ml. This titration continued until the patient achieved satisfactory pain. The patient ultimately achieved excellent pain relief while receiving 11 mcg of ziconotide and 1.32 mg of hydromorphone daily (25 mcg/ml concentration of ziconotide and 3 mg/ml of hydromorphone). Her VASPI score for at-level pain was 12 and for her below-level pain was 8. The patient maintained a relatively low amount of oral opiate consumption (<60 mg of oxycodone daily) for breakthrough pain. The patient has maintained this degree of pain relief for 15 months. The patient continued with the increased intermittent catheterization that occurred with the initiation of intrathecal ziconotide therapy. Otherwise, the patient had no adverse effects from intrathecal ziconotide/hydromorphone mixture.

A visual presentation of the patient's VASPI scores during the course of this treatment strategy is depicted in Figure 1.

Discussion

Although intrathecal medication delivery is a well-recognized tool in the armamentarium of pain management, the use of this therapy sparks much debate among clinicians. Patient selection, trialing methods and medication choices are some the variables that enter into complexity of this therapy. The methodology for this modality is far from standardized.¹⁴ The entrance of ziconotide into this milieu adds to the complexity. The utility of this agent within the context of intrathecal therapy is evolving.¹⁵

Intrathecal therapy for patients with chronic SCI neuropathic pain has been utilized in the past with a similar level of uncertainty regarding medications and techniques. Loubser and Donovan¹⁶ reported a positive effect of intrathecal lidocaine on neuropathic pain in a small double blinded study of 21 spinal cord injured

patients. Slidall *et al*¹⁷ reported on the positive effect of the combination of intrathecal morphine and clonidine in another double blinded study of 15 spinal cord injured patients. This study did not demonstrate a positive effect on pain by either morphine or clonidine in isolation. The decision to proceed with a trial of intrathecal therapy in this patient was undertaken since at least a component of her pain appeared opiate sensitive and since the patient already attempted a significant number of other treatments.

The relative opiate sensitivity/resistance of various types of SCI-associated neuropathic pain (ie above-level, at-level and below-level) is unknown. In the study performed by Siddall *et al*,¹⁷ there was a suggestion of a differential responsive to at-level and below-level pain components. In the patient described in this case report, specific responses to intrathecal medications were observed. Although the patient had adverse effects to intrathecal morphine, her at-level pain syndrome was comparatively sensitive to intrathecal hydromorphone. Conversely, the patient demonstrated a relative resistance with intrathecal hydromorphone to her below-injury pain complaints. This observation suggests that in this patient, the two SCI-pain syndromes occurred because of different mechanisms.

Although intrathecal ziconotide has been utilized to treat SCI-associated pain, this report is the first to detail specifically the description of this medication in this population. The alternative responsiveness of ziconotide and hydromorphone also suggests that the patient's two-pain syndrome utilizes separate processes and possesses differential modulation by these pharmacologic agents. As more spinal cord injured patients are potentially treated with ziconotide, both in isolation and in combination with other intrathecal agents, the relative responsiveness of this medication to the various components of SCI neuropathic pain can be ascertained.

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