

# Trigeminal Neuralgia Relief With Intrathecal Ziconotide

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**Objective:** We report a case of a 59-year-old female with severe TN who experienced satisfactory symptom relief from a single-shot trial of intrathecal ziconotide.

**Method:** Performed a 1 µg single-shot trial of Prialt.

**Results:** Report of satisfaction, no side effects, and complete face and back relief briefly but most notably relief from the TN.

**Discussion:** Ziconotide should be considered for treatment of TN, although further investigation is recommended.

**Key Words:** trigeminal neuralgia pain, ziconotide, intraspinal drug delivery system

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Trigeminal neuralgia (TN) is the most common neuropathic pain syndrome occurring at a rate of 4.3 per 100,000. It is found to be more prevalent in females than males.<sup>1,2</sup> The pain of TN can be sudden and severe, usually unilateral and episodic and it can debilitate sufferers adversely affecting function, quality of life, and health status. Simple triggers such as light touch, drafts of wind, eating, drinking, washing, shaving, applying makeup, or being exposed to temperature extremes may precipitate a painful episode.<sup>2</sup>

Treatments for TN are simple to complex, from medications including anticonvulsants, muscle relaxants, and neuroleptic agents to trigeminal nerve and Gasserian ganglion anesthetic blocks, costly γ knife neuroablative, and microvascular decompression procedures.<sup>3</sup> Carbamazepine (CBZ) remains the most effective treatment but is poorly tolerated with significant side-effects including agranulocytosis and hepatitis.<sup>4,5</sup> There are neither published randomized controlled single-shot trial on the use of intravenous opioids, tricyclic antidepressants, benzodiazepines, antiepileptic drugs nor has the use of the intrathecal (IT) route been reported earlier.<sup>4,6</sup>

Ziconotide (Prialt; Elan Pharmaceuticals, Inc, San Diego, CA) is a nonopioid analgesic agent approved by the Food and Drug Administration for IT administration for

severe, chronic pain in patients appropriate for IT therapy and refractory to other treatments including systemic analgesics, adjunctive therapies, or IT opioids.<sup>7</sup> Ziconotide is a highly polar conopeptide analog that originates from the venom of a fish-eating cone snail called *Conus magnus* and is a hydrophilic molecule that targets the N-type voltage-sensitive calcium channel to inhibit depolarization-induced calcium channels to inhibit depolarization-induced calcium influx and reduce neurotransmitter release from nociceptive afferents.<sup>8</sup>

Safe and effective treatment for TN remains a challenge for healthcare providers and their patients. We report meaningful symptom relief of treatment-resistant TN from a single-shot trial IT injection of ziconotide in a 59-year-old female with unsatisfactory analgesia on high-dose, high-concentration intraspinal opioids for chronic pain at risk for hyperalgesia and granuloma.

## CASE REPORT

KB is a 59-year-old female with a complicated medical history that includes mitral valve stenosis, Lupus, right second division TN, occipital neuralgia, migraines, failed back surgery syndrome, right L3 radiculopathy, T12 herpes zoster, avascular necrosis of the hips, peripheral neuropathy, and multiple drug allergies. She was initially evaluated for pain management in the hospital in 1994 for chronic bladder pain after treatment with Cytexan for Lupus. Longstanding bone pain in her legs was the predominant pain complaint. Medications at the time of consult included long-acting morphine 60 mg by mouth twice a day and tegretol 200 mg 4 times a day for the chronic migraines. At the time of the consult, the patient was given a single-shot IT morphine 0.2 mg trial followed by a second 1 mg trial as an outpatient without success.

In 1997, the patient continued to report high pain levels despite fentanyl 100 µg/h with short-acting oral opioids for breakthrough with tegretol. Having failed high-dose systemic opioids, nonsteroidal anti-inflammatory drugs, neurontin, inderal, mexitol, verapamil, and despiramine, she was admitted to the hospital for a 48-hour epidural morphine trial which provided pain relief to the patient's satisfaction and was subsequently implanted with an intraspinal drug delivery system. At the time of implant, the intraspinal morphine was initiated at 1 mg/24 h preceded by a 0.2 mg bolus dose of preservative-free morphine 10 mg/mL.

Parenteral opioids were tapered off and by May of the same year the IT morphine dose escalated to 4.6 mg/24 h. IT clonidine was added to the morphine to provide relief for profuse sweating thought to be morphine related. Migraine headaches persisted.

First mention of TN was after the tegretol was reduced to 600 mg/d by the endocrinologist with the emergence of right facial pain in all 3 trigeminal distributions, therefore dose was returned to 800 mg/d with resolution of facial pain. In April 1999, after extensive endocrine workup, diagnoses included autoimmune disorder, neuropathic pain, and intractable diaphoresis related to autoimmune dysautonomia. This was resolved after addition of IT clonidine.

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From December 1999 to 2006, the patient's intrathecal morphine sulfate escalated from 16 to 26 mg/d. IT morphine infusate concentrations also increased from 10 to 50 mg/mL. The patient's IT morphine was converted to sufentanil and titrated but this too failed to provide relief at 15 µg/d and therefore KB was restarted on the IT morphine after a few months beginning at 1.5 mg/d rapidly escalating to the 26 mg/d dose.

Interventional treatment for the TN included multiple right supraorbital and right trigeminal ganglion nerve blocks which were helpful only temporarily. She also received right occipital nerve blocks for the occipital neuralgia.

The TN interfered with the ability to chew food or use metal utensils to eat. Peripheral nerve stimulation was discussed with the patient and considered; however, in December 2007, she opted for aggressive treatment with  $\gamma$  knife for TN which provided unsatisfactory results with no relief and new dysesthesias to the oral cavity.

In December 2008, the use of ziconotide was discussed with the patient because of concerns for the risk of hyperalgesia and granuloma with the therapeutic goal of improving analgesia and once stable, the tapering of the intraspinal opioid dose and concentration. Before the IT single-shot trial (SST) of ziconotide, the pump and catheter were examined under fluoro, the side-port accessed and a myelogram performed to show subarachnoid distribution of the dye thus confirming a functioning intraspinal drug delivery system with the IT catheter tip at T12. Morphine dose and concentration at the time of the SST was 26 mg/d and 50 mg/mL, respectively.

The patient then underwent an IT SST of Prialt 1 µg at the L1-T12 level under fluoro that resulted in a rapid decrease in the patient's TN pain from 9 to 6 of 10. "Best pain relief I have ever had," and she was able to touch her face without the sensation of an electric shock. All pain returned after 4 hours of the IT injection. Patient satisfaction with the procedure, pain relief, and side effects were measured at time zero, and the first 24 hours of the procedure. At the postprocedure follow-up appointment, the patient reported satisfaction with the procedure, no side effects and complete face and back relief briefly but most notably relief from the TN. It was decided to add ziconotide to the current IT combination of morphine and clonidine at 1 µg/d.

## DISCUSSION

This is the first reported analgesic response to IT ziconotide for chronic trigeminal neuropathic pain. IT ziconotide is the only treatment that resulted in substantial pain relief for this patient. Ziconotide is well known to result in dose or therapy-limiting side-effects including nausea and dizziness (package insert) therefore, a 1 µg dose was selected to test the patient's responsiveness to the drug without precipitating side-effects.

In 1967, it was postulated focal compression as the primary reason for TN, which accounts for 80% to 90% of TN cases.<sup>9</sup> Xu et al's<sup>10</sup> TN mouse model used a partial infraorbital nerve ligation to investigate TN's cellular mechanism. Results showed partial infraorbital nerve ligation produces persistent changes in peptide neurotransmitter and receptor expression in the caudal medulla region of the brainstem and injures specific neurons in trigeminal ganglia. The authors concluded that injury to peripheral nerves induces both behavioral signs of pain and alters peptide expression in the central nervous system.<sup>10</sup> As mechanisms of trigeminal nociceptive processing is shown to be similar to other somatic nociceptive processing, pharmacologic therapy is believed to function similarly at both levels.<sup>10</sup>

New drugs have been introduced for TN treatment, but CBZ remains the most effective, despite its low tolerability and risk of adverse events.<sup>3,6</sup> Placebo-controlled studies have

shown that anticonvulsants seem to be the most effective group of drugs for TN paroxysmal pain.<sup>2,3,6</sup> CBZ is a tricyclic imipramine that suppresses the intensity and reduces the frequency of paroxysms. However, CBZ is also associated with a number of side effects ranging from mild nausea and drowsiness to agranulocytosis and hepatitis.

If CBZ is not tolerated, the next drug often prescribed is oxcarbazepine (OXC). OXC is a daughter drug of CBZ, but its pharmacokinetics are less complex.<sup>3</sup> Four double-blinded, crossover studies evaluated OXC's efficacy and tolerability as compared with CBZ.<sup>3,6</sup> Results showed that OXC is as efficacious in decreasing the number of paroxysms with fewer reported adverse events.<sup>3</sup> Other medications investigated, such as baclofen and lamotrigine, seemed to show positive results, but were not as effective as CBZ.<sup>2,3,6</sup> Small open-label studies have evaluated other antiepileptic drugs, such as clonazepam, gabapentin, and valproate; although, results showed no significant therapeutic benefit. Intravenous drugs, lidocaine and fosphenytoin, have been suggested, as well as for the use of intravenous opioids, tricyclic antidepressants, benzodiazepines, antiepileptic drugs, or nonopioid analgesics, but no randomized clinical trials have been completed.<sup>2,6,9</sup>

Ziconotide is the most extensively studied analgesic agent for IT therapy.<sup>7</sup> The pharmacokinetics of IT ziconotide were investigated in patients with chronic pain at various dose levels (1, 5, 7.5, and 10 µg) at a volume of 1 mL over 1 hour.<sup>11</sup> Results showed peak concentration of blood and cerebral spinal fluid were linear and proportional to the dose.<sup>11</sup> Terminal elimination half-life was 4.2 to 5.3 hours and the median volume of distribution across dose groups was 99 mL (mean 150 mL), showing a volume of distribution that is consistent with the physiologic volume of the IT space. Although this suggests that it freely diffuses within the cerebral spinal fluid, no studies have found how long it takes for a cerebral ziconotide level to be obtained. This would answer the question of whether or not a single IT injection could reach the brainstem and produce effects in the timeframe that it did for this patient.<sup>8,11,12-18</sup>

If pharmacologic treatments do not provide satisfactory pain relief from TN, surgical treatment is often offered. Gamma knife surgery is a noninvasive technique that focuses a beam of radiation at the trigeminal root in the posterior fossa.<sup>2</sup> This surgery was unsuccessful for our patient.

TN continues to be a treatment challenge for physicians to successfully manage and remains the cause of great suffering, impaired function, and quality of life for afflicted patients. It is unknown whether ziconotide would be beneficial as a single agent or whether its benefit is a result of an interaction between other medications. It is gaining recognition for its ability to provide neuropathic pain relief and is actively being researched to treat a variety of chronic pain conditions. At the time of our patient's trial, she received CBZ 300 mg/d and IT morphine (26.016 mg/d). Neither had provided relief alone, nor in combination, before addition of ziconotide.

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