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Short-Term Outcomes of a High-Volume, Low-Concentration Bolus Starting Dose Technique With Ziconotide: A Case Series

David Lindley, DO

ABSTRACT

Background and Objectives: There have been numerous recommendations for a starting dose of intrathecal ziconotide. The therapy remains underutilized partially due to reports of inefficacy and/or intolerance. This study describes short-term outcomes of a high-volume, low-concentration bolus (HVLC-B) ziconotide starting dose technique for patients with chronic spine pain. Intrathecal pumps are available with a Patient Therapy Manager (PTM), or patient-controlled intrathecal bolus device. Commonly published recommendations for a bolus dose has been 10% of the daily dose. This article describes an inversion of the traditional 10% rule-of-thumb. This article describes using the basal rate at a lowest programmable dose and utilizing the bolus for the majority of the medication delivery. Such an inversion may be considered a high volume bolus. The lowest commercially available concentration of ziconotide from the manufacturer is 25 mcg/mL. Pope and Deer (*Neuromodulation*, 18, 414–420 [2015]) described use of a dilution down to 5 mcg/mL. For purposes of this article, such dilutions to one-fifth of the commercially available solution are considered sufficiently dilute to qualify for the term "low concentration." Furthermore, the patients in this analysis received dilutions down to one-fiftieth of the lowest commercially available solution.

Materials and Methods: A case series of patients with chronic spine pain with or without radicular pain received a starting dose intrathecal ziconotide regimen based on a specific HVLC-B technique. Efficacy, tolerability, and pump settings are reported and analyzed.

Results: In total, 17 patients were identified who started ziconotide with the specified HVLC-B starting regimen. One of the 17 patients reported side effects that led to discontinuation of the therapy, although the side effect was not typical of ziconotide but rather likely attributable to other medications the patient was taking. Fifteen of the 17 reported improved pain control with intrathecal ziconotide. Sixteen of the 17 patients remained on intrathecal ziconotide throughout the 4.7-month average follow-up period. One patient who failed to obtain pain relief chose to remain on the therapy because of reported resolution of lower limb numbness.

Conclusions: The HVLC-B starting regimen was effective and well tolerated in this short-term study of patients with chronic spine pain. More studies are needed to better elucidate long-term outcomes in larger patient populations.

Keywords: Chronic pain, intrathecal, nonopioid, ziconotide

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INTRODUCTION

Cone snails are venomous species found in the Atlantic and Pacific oceans. There are 50–200 different peptides in the venom of each species of cone snail (1). A laboratory at the University of Utah led by Baldomero Olivera has studied many of these conotoxins. With help from then undergraduate student Michael McIntosh, Olivera discovered one particular conotoxin—found in the cone snail *Conus magus*—that has a paralytic motor effect in fish. It was later discovered that this same receptor in humans is responsible for pain transmission. A synthetic version of the *C. magus* peptide has since been successfully developed as a pain medication for humans. This agent, called ziconotide, is a highly water-soluble peptide that consists of 25 amino acid units, which includes three cysteine bonds that help maintain the tertiary structure.

Ziconotide inhibits the N-type voltage-sensitive calcium channel. Calcium channels of various types affect different nerve types. For example, in humans, vascular structures use the L-type voltage-sensitive calcium channel, whereas N-type voltage-sensitive calcium channels are involved with pain fiber transmission in the spinal cord. In fact, both ziconotide and μ-agonists (opioids) inhibit the N-type voltage-sensitive calcium channel,

Address correspondence to: David Lindley, DO, Dozier Pain Management, 2401 North Treadaway Blvd, Abilene, TX 79601, USA. Email: davidalindleydo@gmail.com

Dozier Pain Management, Abilene, TX, USA

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though ziconotide is not an opioid. Ziconotide is a direct inhibitor of the N-type voltage-sensitive calcium channel, whereas opioids inhibit this same receptor indirectly by way of activating a μ-receptor that then inhibits the N-type voltage-sensitive calcium channel by way of a G protein mechanism. By inhibiting preganglionic N-type voltage-sensitive calcium channels, the transmission of the noxious signal from the first-order neuron to the second-order neuron is inhibited at the level of the spinal cord.

Nonopioid Treatment of Chronic Nonmalignant Pain

The treatment of chronic nonmalignant axial pain can be challenging, particularly given the recent push in the United States toward nonnarcotic therapies. Intrathecal delivery mechanisms can minimize and control the delivery of narcotic medications. However, nonnarcotic intrathecal therapy is available with ziconotide.

As peptides, conotoxins are relatively inactive when injected into laboratory mice by intraperitoneal route. However, when injected into laboratory mice by intracranial route, a diverse array of pharmacologic activity is observed. Also, peptide drugs are subject to digestive enzymes when ingested orally. Ziconotide has been developed as an intrathecal route medication (2).

Ziconotide, one of just three US Food and Drug Administration-approved intrathecal medications for chronic pain (the other two being baclofen and morphine), has been clinically available for years, but widespread awareness of its therapeutic and clinical use has been limited. In addition, published studies of ziconotide use describe dosing techniques associated with a high side effect profile (3–6). Similarly, the ziconotide package insert describes a rate of 93% side effects for ziconotide-treated patients. Common side effects include side effects, including dizziness, nausea, confusion, and nystagmus (7).

Determining Effective Dosing for Ziconotide

Patients' lives, activity levels, and analgesic requirements vary day to day. It has been common to base ziconotide dosing on basal rate dosing regimens, which do not allow flexibility based on patient needs. A regimen based on a patient-controlled bolus may be beneficial. In addition, data demonstrate limited spread of drugs delivered intrathecally (7,8), with spread improving based on volume and rate of delivery. Thus, a low-concentration, high-volume, patient-controlled bolus dose of intrathecal ziconotide may improve efficacy and tolerance of the therapy.

There have been numerous recommendations for intrathecal ziconotide starting doses. For example, the Polyanalgesic Consensus Committee suggests starting at 0.5–1.2 μg/day, followed by dose titration of 0.5–1 μg/day every several days (9). Also, McDowell has described patient-controlled bolus dosing set at approximately 10% of the basal rate, linking the dosing regimen more to basal rate than patient-controlled bolus dosing (10). In addition, no specific guidelines for starting concentration, volume, or rate of bolus delivery recommendations exist. This retrospective case series analyzed the efficacy and tolerance of a starting dose strategy that employs a high-volume, low-concentration bolus (HVLC-B) dosing technique of ziconotide using a Medtronic intrathecal pump and patient therapy manager in 17 patients with axial pain.

MATERIALS AND METHODS

A data search of electronic health records (EHRs) was conducted in a rural pain clinic from December 1, 2017, through December 1, 2018. Because exact characteristics of dosing and pain scores can vary over time, this report is based on an analysis of the EHRs at 1 point in time (December 1, 2018).

Data presented include etiology of pain, duration of pain before initiation of therapy, pain scores before and after initiation of therapy, average follow-up time, subjective functional changes or adverse effects as reported by the patient, pump size, drug concentration, basal rate, patient-controlled bolus dosing, rate of bolus delivery, whether the patient is still on therapy, and reasons for discontinuation (if applicable).

Statistical Methods

Patient-reported pain scores and percentage relief are reported. If a patient recorded a pretherapy pain score and posttherapy pain score that did not mathematically equate to the given percentage relief, the numbers are reported that way. For example, if patient stated that his or her pain was 10 of 10 before therapy and 2 of 10 since therapy but describes the pain relief as 70% improved, it will be described as reported by the patient. Data were entered into a spreadsheet program and simple average formulas were used to analyze the data.

Inclusion Criteria

Patients were included if they had chronic nonmalignant axial spine pain with or without radicular or extremity pain. The dosing technique for intrathecal ziconotide required discontinuing any opioid therapies at least ten days before pump implant; implanting a 40-mL intrathecal pump (Medtronic SynchroMed II model 8637-40; Minneapolis, MN, USA); and starting a regimen of intrathecal ziconotide at 0.5 μg/mL, with a 0.024-μg/day basal rate and a 0.25-μg on-demand patient-administered bolus (using the Medtronic myPTM Personal Therapy Manager) up to three times per day. Settings were changed as necessary at subsequent visits, but the starting regimen was as described.

Preparation of the drug was by a hospital pharmacist under a hood. The pharmacist obtained 0.8 mL of ziconotide base solution at a concentration of 25 mcg/mL. The resulting 20 mcg was further diluted with preservative free normal saline to a concentration of 0.5 mcg/mL in 40 mL. Although ziconotide contains three disulfide bonds, these are apparently not fragile enough to be disturbed by dilution. Attenuated effect due to dilution was not observed in this study nor in a study by Pope which also used dilute concentrations (3). Also, the package insert for ziconotide describes end-user dilution of stock drug with preservative free normal saline (7).

Exclusion Criteria

Patients who had previously been implanted with opioid pumps and transitioned to ziconotide were not included. Patients whose primary cause of pain was malignancy or who had nonaxial pain were also excluded. One patient was excluded because the pump was explanted 42 days after implant secondary to complications of an adjacent melanoma scar.

RESULTS

The EHR review identified 17 patients who had undergone ziconotide intrathecal pump implant and started on the specified starting dose regimen (HVLC-B) technique. Of these 17 patients, one was excluded because of complications involving a melanoma scar soon after implant that led to explant of the pump after 42 days.

Of the 17 cases identified, 11 (65%) were implanted for an indication that included postspine surgery syndrome (one cervical and back in the same patient, two cervical, eighth back). Fourteen patients (82%) were implanted for indications that involved lumbar pain. Four patients (24%) were implanted for indications that involved thoracic pain, and another four (24%) were implanted for indications that involved cervical pain. Some patients had pain in more than one area. Sixteen patients (94%) had a documented history of having tried opioids for their pain.

The average follow-up time was 4.7 months as patients were at different points in the therapy. Statistics were calculated at this average follow-up time to analyze the concentration and dosing parameters resulting after the follow-up visits, titrations, and refills that occurred during this early titration phase of treatment.

At time of last follow-up, the average concentration of ziconotide was 1 μg/mL. The average basal rate was 0.19 μg/day. The average myPTM bolus amount was 0.27 μg. The average bolus volume was 0.41 mL. The average velocity of bolus infusion was 0.0147 mL/min. Only one patient's pump setting was changed from the default maximum bolus rate. The average total dose of intrathecal ziconotide, including basal rate and bolus doses used, was 0.736 μg/day (range, 0.024–2.379 μg). One patient (patient 10) decided to continue intrathecal ziconotide therapy despite reporting no pain relief. His reasoning was that intrathecal ziconotide therapy had resolved his lower limb numbness.

Of the 17 patients who met the inclusion criteria for this retrospective study and 16 (94%) remained on the drug at the time of last analysis. The average pain relief for all 17 patients was 71%; median pain relief was 75%.

Two patients (11.7%) reported side effects. Of these, one (5.8%) asked to discontinue the therapy because of easy bruising. The ziconotide package insert reports no reported side effect of bruising in 1254 patients with a mean duration of 193 days of infusion at an average dose of 17.6 μg/day. The patient in my study was on both clopidogrel and aspirin but did not feel that the blood thinners had caused the side effect. Sixteen of the 17 patients remained on intrathecal ziconotide therapy through the end of the time period studied.

The other reported side effect was headache that occurred after bolus. Despite this side effect, that patient requested an increase in the patient-controlled bolus frequency from 3/day to 4/day. To address the headache that occurred after bolus, the rate of bolus delivery was decreased from 31 min to 90 min (bolus rate decreased from 0.0161 mL/min to 0.0056 mL/min). This bolus rate change resulted in resolution of the bolus-induced headache.

Most often, the highest velocity of bolus infusion was used: 0.016 mL/min (the default with the pump model used in this study). A fast bolus rate is likely a benefit because it helps the medication spread around the spinal cord. It is worth noting, however, that when using larger volumes, the bolus can sometimes spread the medication around too much. In this study, the bolus rate was decreased in one patient. This was a relatively short (157 cm [5 feet 2 in]) female with relatively small body habitus (body mass index of 20). In this case, decreasing the bolus rate of delivery resolved the headache side effect. Although her area of pain included the neck and post-neck surgery syndrome, it is possible that the ziconotide reached too far cephalad and decreasing the rate of delivery limited the delivery more to the target cephalad levels.

Patient characteristics are outlined in Table 1, and pump settings are outlined in Table 2. Generally, at the time of each assessment, if the drug concentration was inadequate to achieve at least a 30-day refill interval, then concentration was increased. Based on pump characteristics at the time of data collection, the average time until the pump reservoir was empty was 4.16 months (range, 0.58–27.78 months). Based on clinical observation of stability by the author, pumps were refilled at 2.5–3 months even if the volume had not been depleted by that time.

DISCUSSION

This novel HVLC-B starting strategy used a low dose that was well tolerated. The high-volume, high-velocity, low-concentration bolus is proposed to provide adequate spread along the spine and contribute to efficacy despite the low overall mass dose.

For any given mass of drug, this strategy would use a higher volume of medication. The higher volume, delivered at a relatively high velocity by way of patient-administered bolus, will theoretically spread more extensively in the cerebrospinal fluid. Using intermittent, relatively fast delivery, bolus dosing would theoretically lead to more widespread distribution of the drug and potentially greater efficacy. In other words, improved distribution of the drug at the site of action in the spinal cord may dampen afferent input while not allowing enough mass of drug to cause tolerability issues.

For purposes of comparison, consider the following example. A 25-μg/mL concentration with a basal rate of 0.25 μg/day will deliver 0.01 mL of drug over 24 hours, a delivery rate of 0.00000694 mL/min. In contrast, a 0.5-μg/mL concentration with a 0.25-μg bolus will deliver 0.5 mL of drug over 31 min, a delivery rate of 0.016 mL/min—a volume 50 times larger delivered at a rate more than 2300 times faster. For the same microgram dose, the larger volume and higher rate of delivery may have a significant impact on efficacy while minimizing side effects because of the low overall microgram dose.

The effect may be analogous to the adage that three nodes of Ranvier must be blocked to inhibit a nerve. In this case, the more diffuse spread of medication along the spinal cord may better inhibit nociceptive pathways and cover the divergence of afferent nerves. The dose, however small it seems, is still supraphysiologic. The lower-dose, higher-volume, higher-velocity strategy may be more effective because it allows more widespread segmental spinal cord spread, including enhanced anterior and posterior spinal cord spread, as has been demonstrated in pig models (3).

Earlier case series by Hayek (4) used relatively higher dosing strategies, as well, and found limitations from side effects. Also, some published studies describe the use of ziconotide predominately in a population in which intrathecal therapy with other agents had already failed rather than one in which ziconotide was used as a first-line intrathecal agent, as described by published algorithms (4,5). These prior reports provided little information about volume or rate of drug delivery. A similar dosing strategy was described Pope and Deer using a flex dose bolus regimen (3). The flex regimen is beneficial because it ensures compliance and

Table 1. Patient Characteristics.

Patient no.	Age at time of data collection* (years)	Gender	Duration of pain before implant (years)	Indication for implant	Tried opioids before pump implant?	Pain score before implant	Pain score at most recent visit	Improvement (%)
1	54	F	9	Thoracic pain, thoracic disc herniation, low back pain, lumbar stenosis, RA	Yes	3.5/10 at best, 8/10 on average, 10/10 at worst	4/10 average	50
2	85	M	5	Neck pain, post-neck surgery syndrome, low back pain, post-back surgery syndrome	Yes	9–10/10	2–3/10	74
3	68	F	32	Low back pain, post-back surgery syndrome (multiple lumbar surgeries)	Yes	6–10/10	0/10	100
4	53	F	20	Lumbosacral pain, lumbosacral radiculopathy, immune-mediated polyarthralgia	Yes	8/10	0/10	80
5	88	M	2.5	Low back pain, lumbar stenosis, lumbar degenerative disc disease	Yes	7–10/10	1/10	88
6	82	F	18	Low back pain, lumbar stenosis	yes	2/10 at rest; 7–10/10 standing	0/10	95
7	85	M	5	Low back pain, post-back surgery syndrome, lumbar radiculopathy, lumbar spondylosis, lumbar degenerative disc disease	No	0/10 at rest; 7–8/10 pain when he got out of bed in the morning; 4/10 immediately upon standing, 9/10 after standing 30 min	0/10	90
8	89	F	10	Thoracic pain, thoracic degenerative disc disease	Yes	10/10 even at rest	0	100
9	68	F	16	Low back pain, post-back surgery syndrome	Yes	7–10/10, average 8.5/10	5	40
10	39	M	12	Low back pain, lumbar radiculopathy, post-back surgery syndrome	Yes	8–10/10	8–10/10	0
11	62	F	33	Low back pain, post-back surgery syndrome	Yes	6–10/10	0/10	100
12	55	M	3	Neck pain, cervical radiculopathy, post-neck surgery syndrome	Minimally	8/10	3/10	60
13	72	M	10	Thoracic pain, post-back surgery syndrome, low back pain	Yes	7/10	1–2/10	75
14	74	F	28	Low back pain, post-back surgery syndrome	Minimally	10/10	2/10	75
15	72	F	1.3	Chronic neck pain, cervical degenerative disc disease, chronic thoracic pain, thoracic spondylosis, chronic low back pain, post-back surgery syndrome	Yes	10/10	0–2/10	93
16	76	M	35	Low back pain, lumbar stenosis, lumbar degenerative disc disease	Yes	4–8/10	1–4/10	65
17	53	F	44	Neck pain, cervical radiculopathy, post-neck surgery syndrome	Yes	7–15/10†	6/10	30

F, female; M, male; RA, rheumatoid arthritis.
*Date of data collection was December 1, 2018.
†Patient reported 15/10 pain score to describe pain intensity.

Table 2. Intrathecal Ziconotide Pump Settings.

Patient No.	Date of implant	Time since implant (mo)	Pump size (mL)	Ziconotide concentration (μg/mL)	Ziconotide basal rate (μg/d)	Bolus dose (μg)	Bolus duration (min)	Bolus volume (mL)	Bolus rate (μg/min)	Bolus rate (mL/min)	Avg Bolus use (μg/d)	Avg dose per day (Basal + Bolus) (μg/d)	Still on ziconotide?	Reason for discontinuation
1	Dec 2017	12	40	0.5	0.100	0.30	37	0.60	0.0081	0.0162	0.6273	0.7273	No	Easy bruising
2	Feb 2018	10	40	0.5	0.024	0.30	37	0.60	0.0081	0.0162	0.0200	0.0440	Yes	N/A
3	Mar 2018	9	40	0.5	0.240	0.15	19	0.30	0.0079	0.0158	0.0059	0.2459	Yes	N/A
4	Mar 2018	9	40	0.5	0.024	0.30	37	0.60	0.0081	0.0162	0.0000	0.0240	Yes	N/A
5	Apr 2018	8	40	1.0	0.550	0.31	60	0.31	0.0052	0.0052	0.3100	0.8621	Yes	N/A
6	May 2018	7	40	2.5	0.250	0.25	6	0.10	0.0417	0.0167	0.5769	0.8269	Yes	N/A
7	May 2018	6	40	0.5	0.350	0.25	31	0.50	0.0081	0.0161	0.0137	0.3637	Yes	N/A
8	Jul 2018	4	40	1.0	1.000	0.15	10	0.15	0.0150	0.0150	0.0000	1.0000	Yes	N/A
9	Aug 2018	4	40	2.5	0.250	0.38	10	0.15	0.0380	0.0152	1.3843	1.6343	Yes	N/A
10	Sep 2018	2	40	5.0	0.250	0.45	6	0.09	0.0750	0.0150	2.3786	2.6286	Yes	N/A
11	Sept 2018	2	40	0.5	0.024	0.25	31	0.50	0.0081	0.0161	0.3077	0.3317	Yes	N/A
12	Oct 2018	2	40	0.5	0.024	0.30	37	0.60	0.0081	0.0162	0.2500	0.2740	Yes	N/A
13	Oct 2018	1	40	0.5	0.024	0.25	30	0.50	0.0083	0.0167	1.1250	1.1490	Yes	N/A
14	Oct 2018	1	40	0.5	0.024	0.25	31	0.50	0.0081	0.0161	0.3409	0.3649	Yes	N/A
15	Nov 2018	1	40	0.5	0.024	0.25	31	0.50	0.0081	0.0161	0.3947	0.4187	Yes	N/A
16	Nov 2018	1	40	0.5	0.024	0.25	31	0.50	0.0081	0.0161	0.4063	0.4303	Yes	N/A
17	Nov 2018	1	40	0.5	0.024	0.25	90	0.50	0.0028	0.0056	0.7115	0.7355	Yes	N/A

N/A, not applicable.

use of the therapy, whereas the bolus technique is beneficial in allowing patient input on the titration and day-to-day dosing. The HVLC-B dosing strategy appears to be efficacious and well tolerated.

Similar to this study, ziconotide was used as a first-line intrathecal agent in a 2017 study by Prusik (11) that employed basal rate dosing starting at 1.2 μg/day. The study followed the patients for an average of 15.5 months and found that more than 50% of patients reported at least 30% relief. The concentration of ziconotide was not reported.

Limitations

This study was limited by its case series design. It has no prospective design or comparison group. Larger, prospective, randomized, multisite studies are needed to validate the findings of this small, single-site analysis.

CONCLUSION

The HVLC-B starting dose technique with ziconotide is well tolerated and effective for chronic nonmalignant axial pain. Efficacy is most logically explained by low mass doses of drug delivered at a higher volume, with a higher rate of delivery and greater spinal cord spread.

It is possible that volume and rate of delivery are important determinants of efficacy for ziconotide. In fact, they may be as important or more important than mass of drug delivery. Lower overall doses can be achieved by using higher-volume bolus delivery. It is also possible that a small, mildly supraphysiologic inhibition of the N-Type calcium channel is as effective and better tolerated than massive supraphysiologic inhibition.

Although the sample size in this study is small, this HVLC-B strategy appears to be promising. The use of this starting dose technique may facilitate more patients benefitting clinically from the therapy and thwart more widespread opioid use. Prospective and randomized studies would clarify this hypothesis. In addition, the discussion of intrathecal drug starting techniques could be broadened to include parameters such as volume, bolus volume, and rate of bolus.

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Authorship Statements

Dr. David Lindley designed and conducted the study including design of inclusion criteria, database identification of patients, data collection and data analysis. Dr. David Lindley provided all intellectual input for the prepared manuscript draft. Dr. David Lindley thanks Rochelle Wagner, PhD, an employee of TerSera Therapeutics and LoAn K. Ho, PharmD, of Wesley Enterprise, Inc., for their help with medical writing and editorial support.

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COMMENTS

This case series examines the clinical benefit of low concentration high volume bolus dosing of ziconotide. The results suggest that this dosing strategy provides for a larger distribution in the cerebrospinal fluid and is associated with a lower side effect profile and greater analgesic benefit. Further studies are warranted to further elucidate the ideal dosing strategy for ziconotide.

Lawrence Poree, MD, PhD
San Francisco, CA USA

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Tolerability is an important factor in allowing patients to remain on ziconotide during the titration to efficacy phase. We know that slow titration is important, but wider drug dispersal appears to be one of the key factors in achieving efficacy now that our understanding of CSF dynamics has improved. This scheme of high-volume-low-concentration certainly merits greater exploration.

Gladstone C McDowell II, MD
Columbus, OH USA

