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Observational Study

Intrathecal Ziconotide and Opioid Combination Therapy for Noncancer Pain: An Observational Study

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Background: Intrathecal ziconotide is used to manage severe chronic pain. Although ziconotide is approved by the US Food and Drug Administration for monotherapy, it is sometimes used in combination with other intrathecal drugs for the management of intractable pain conditions in clinical practice.

Objectives: Evaluate the safety and tolerability of ziconotide combination therapy.

Study Design: A retrospective, observational study.

Setting: A single center.

Methods: Patients with severe chronic pain of noncancer origin who were receiving inadequate analgesia with intrathecal opioid therapy (with or without intrathecal adjuvants) and who had ziconotide added to their intrathecal regimens were included. Patient characteristics, intrathecal ziconotide doses, concomitant intrathecal and systemic drug use, visual analog scale pain scores, Oswestry Disability Index scores, mini-mental status examination scores, neurological examination results, clinical observations (including adverse event reports), and equipment complications were reviewed for 12 weeks after ziconotide initiation.

Results: Sixteen patients were identified. Ziconotide was initiated at a dose of 0.5 mcg/d and titrated to a mean dose of 2.64 mcg/d at week 12. Intrathecal opioids were hydromorphone (n=7), morphine (n=5), fentanyl (n=3), and sufentanil (n=1). Adverse events were noted in one patient, who reported increased depression and pain during combination therapy; ziconotide treatment was discontinued, and all adverse events resolved over a 4-week period. Substantial pain relief (≥4-point decrease in visual analog scale score) was reported in 3 of 15 patients (20.0%) and increased functional capacity was evident in 3 of 15 patients (20.0%).

Limitations: A retrospective study with a limited number of patients from a single center.

Conclusion: Results from this observational study suggest that combination intrathecal ziconotide and opioid therapy may be a safe and potentially effective treatment option for patients with refractory chronic pain. Controlled, prospective clinical trials to evaluate ziconotide combination therapy are needed.

Key words: Ziconotide, intrathecal, chronic pain, opioids, combination therapy, nonopioid analgesic

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Approximately 9% of the adult population in the United States experiences moderate to severe chronic pain of noncancer origin (1). This pain disorder has been shown to lead to decreased physical, psychological, and social well-being (2). Noncancer chronic pain remains a treatment challenge for many clinicians and patients. Some patients benefit from conservative interventions (eg, physical therapy, oral opioids), whereas others require more aggressive interventions such as intrathecal analgesics. For patients with neuropathic or nociceptive pain, the use of targeted intrathecal drug delivery may be advantageous because medication is delivered directly to the spinal receptors, allowing action at the receptor level with markedly reduced systemic exposure (3). Thus, adverse events may be minimized at equipotent analgesic doses.

Currently, ziconotide (PRIALT®, ziconotide intrathecal infusion, Elan Pharmaceuticals, Inc., 800 Gateway Blvd., South San Francisco, CA 94080) and morphine are the only drugs approved by the United States Food and Drug administration for intrathecal pain therapy; these agents are approved for monotherapy use only. Ziconotide is a nonopioid analgesic; results from animal studies suggest that ziconotide inhibits neurotransmission from primary nociceptive afferents in the dorsal horn of the spinal cord by binding to and blocking N-type voltage-sensitive calcium channels (4-6). Opioids, such as morphine, exert their antinociceptive effects directly by interacting with μ-opioid receptors and indirectly by inhibiting N-type calcium channels (7-10).

According to the 2007 Polyanalgesic Consensus Conference expert panel members, monotherapy treatment with ziconotide, morphine, or hydromorphone is recommended as a first-line intrathecal treatment option for chronic pain (11). If first-line treatments fail to provide adequate pain relief, approaches on algorithm lines 2, 3, and 4 include ziconotide in combination with opioids (with or without intrathecal adjuvants). When delivered in combination, ziconotide and opioids may produce additive analgesic effects because of their different mechanisms of action. This theory is supported by 2 recent open-label studies that revealed that combination therapy with intrathecal morphine and ziconotide produced greater pain relief than did the use of either analgesic alone (12,13). In addition, results of these studies suggest that combination intrathecal ziconotide and morphine therapy is generally safe; treatment-emergent adverse events were similar to adverse events observed during studies of intrathecal monotherapy treatment with ziconotide (14-16) or morphine (17-19). The safety and effectiveness of intrathecal ziconotide in combination with opioids (with or without intrathecal adjuvants) were also investigated in a retrospective chart review (20). In that study, mean pain scores improved by 43% after the initiation of ziconotide treatment, and 10% of patients experienced adverse events.

Results from these 2 small open-label studies and one retrospective study suggest that combination ziconotide and opioid therapy may be effective and well tolerated; however, safety data are limited. In the current retrospective study, the safety and tolerability of intrathecal ziconotide in combination with intrathecal opioids were investigated in patients with chronic noncancer pain.

Methods

A retrospective, observational study was performed by reviewing medical records from a single center. Although our institutional review board was consulted, it did not review the study because the study is retrospective in nature. Patients with severe chronic pain of noncancer origin who were treated between October 1, 2006, and February 28, 2007; who experienced inadequate analgesia with stable oral opioid and intrathecal therapy (an intrathecal opioid with or without adjuvant intrathecal drugs); and who had ziconotide added to their intrathecal regimens were identified and included in the analysis. Inadequate analgesia was defined as a maintained visual analog scale (11-point scale, 0 representing no pain and 10 representing the worst pain imaginable) pain score of ≥ 8. Oral opioid and intrathecal therapies were considered stable if no dosing adjustments were made for at least 2 weeks before the initiation of ziconotide. Patients were required to have an implanted programmable Medtronic SynchroMed® infusion system (Medtronic, Inc., 710 Medtronic Parkway, Minneapolis, MN 55432) with 2-piece catheters. Patients aged < 21 or > 80 years were excluded from the analysis. In addition, patients were excluded if they added or discontinued any oral agent or had dosing adjustments to intrathecal drugs other than ziconotide during the 12 weeks that followed ziconotide initiation.

Patient medical records were reviewed for the period of up to 12 weeks after the initiation of ziconotide. Data were collected regarding intrathecal ziconotide doses, intrathecal opioid and adjuvant drug use, oral

medication use, visual analog scale scores, mini-mental status examination scores, neurological examination results (including tests of short- and long-term memory and examinations of cranial nerves, reflexes, motor function, sensation, coordination, and cerebellar function), clinical observations (including adverse event reports), and equipment-related complications (eg, catheter failure, pump malfunctions).

Safety was assessed by reviewing adverse event reports, mini-mental status examination scores, and neurological examination results recorded at each clinic visit. Effectiveness was assessed as the change from baseline (ie, before the initiation of ziconotide) to Week 12 in visual analog scale score. A decrease in visual analog scale score of ≥ 4 points was considered to be substantial pain relief, a decrease in visual analog scale score of 1 to 3 points was considered to be mild to moderate pain relief, a change in visual analog scale score of 0 indicated no change in pain, and an increase in visual analog scale score indicated increased pain. Functional capacity, which was recorded at each pump refill, was evaluated by analysis of the "walking" and "sitting" parameters of the Oswestry Disability Index (ie, the extent to which pain interfered with each patient's ability to walk and sit). All results were summarized descriptively.

Results

Sixteen patients (5 men, 11 women) were identified; pain diagnoses are summarized in Table 1, and concomitant intrathecal opioid and adjuvant drugs are summarized in Table 2. The mean age of the patients was 62 years, patients had experienced chronic pain for an average of 15.8 years, and the mean duration of intrathecal opioid therapy before ziconotide treatment began was 3.8 years. For all 16 patients, ziconotide was initiated at a dose of 0.5 mcg/d; at Week 12 (n=15), the mean ziconotide dose was 2.64 mcg/d (range, 0.61–5.7 mcg/d). Concomitant intrathecal opioids were hydromorphone, morphine, fentanyl, and sufentanil. The mean pump refill interval was 26.2 days (range, 7–28 days).

Fifteen of 16 patients (93.8%) remained on combination intrathecal ziconotide and opioid therapy at Week 12. One patient, who had a remote history of depression, reported increased pain and depression 2 weeks after the initiation of ziconotide (ziconotide dose, 0.61 mcg/d; hydromorphone dose, 6.3 mg/d). Intrathecal ziconotide was discontinued, and the patient received treatment for depression. All adverse events in this patient resolved over a 4-week period, and no sequelae were reported. No other adverse events were reported by this or any other patient, and no

Table 1. *Patient diagnoses (N=16)*

Diagnosis[a]	Patients, n (%)
Lumbar radiculitis	14 (87.5)
Lumbar postlaminectomy syndrome	8 (50.0)
CRPS 1 or 2	4 (25.0)
Lumbosacral disc disease	4 (25.0)
Low back pain	2 (12.5)
Postherpetic neuralgia	2 (12.5)
Spinal stenosis	2 (12.5)
Lumbar sprain/strain	1 (6.2)
Neuritis/neuralgia	1 (6.2)
Thoracic back pain	1 (6.2)

Abbreviation: CRPS, complex regional pain syndrome.
a Patients could have more than one diagnosis.

Table 2. *Intrathecal opioid use and intrathecal adjuvant drug use (N=16)*

	Patients, n (%)	Mean Dose
Intrathecal opioid		
Hydromorphone	7 (43.8)	4.6 mg/d
Morphine	5 (31.2)	5.2 mg/d
Fentanyl	3 (18.8)	990 mcg/d
Sufentanil	1 (6.2)	1100 mcg/d
Adjuvant intrathecal drug		
Bupivacaine	4 (25.0)	0.5 mg/d
Clonidine	3 (18.8)	113 mcg/d
Baclofen	1 (6.2)	14 mcg/d

clinically important changes were noted for any other safety parameter.

Among the 15 patients who completed 12 weeks of ziconotide combination therapy, 3 (20.0%) reported substantial pain relief, 4 (26.7%) reported mild to moderate pain relief, 6 (40.0%) reported no change in pain, and 2 (13.3%) reported increased pain (Table 3). Results from the Oswestry Disability Index revealed that 3 of 15 patients (20.0%) were able to walk longer distances and sit for longer periods of time.

No instances of catheter failure or occlusion, pump failure, or discrepancy of pump volume at the time of refill were reported.

Discussion

This retrospective medical record review study provided a preliminary evaluation of the use of ziconotide as an adjuvant to intrathecal opioids. Combination intrathecal ziconotide and opioid therapy appeared safe and well tolerated in these patients. Although these results are consistent with those from 2 open-label studies of combination ziconotide and morphine therapy (12,13), the patients in the current study were receiving a variety of opioid and adjuvant drugs, which may better reflect the patient population typical of a private practice pain clinic. Adverse events were reported for only one patient (6.2%) and resulted in that patient's discontinuation of ziconotide treatment. All of the patient's adverse events resolved over a 4-week period, and no sequelae were reported. This patient's experience showed that ziconotide can be discontinued quickly if adverse events occur, without causing withdrawal effects.

Clinical trials have demonstrated that ziconotide is better tolerated when a low starting dose and a slow titration schedule are used (14-16). The starting dose (0.5 mcg/d) and the maximum dose at Week 12 (5.7 mcg/d) in the current study were substantially lower than the maximum recommended starting dose (2.4 mcg/d) and the maximum recommended dose after 3 weeks of titration (19.2 mcg/d) outlined in the ziconotide prescribing information (21). It is possible that the low incidence of adverse events observed in the current study was related to the low starting dose and slow titration of ziconotide; adverse events led to ziconotide discontinuation more often in clinical trials that used more aggressive dosing and titration strategies (15,16) than in a trial that used a slower titration strategy (14).

In this study, the addition of intrathecal ziconotide to an existing intrathecal opioid regimen produced improvements in pain relief in 46.7% of patients; notably, these patients had pain that was markedly refractory to other treatments. Because there were no changes

Table 3. *Change from baseline to week 12 in visual analog scale pain score[a] (n=15)*

Concomitant Intrathecal Drug(s)	Score Decreased ≥4 Points, n (%)	Score Decreased 1-3 Points, n (%)	Score Unchanged, n (%)	Score Increased, n (%)
Fentanyl	0	1 (6.7)	1 (6.7)	0
Hydromorphone	1 (6.7)	1 (6.7)	2 (13.3)	0
Sufentanil	0	0	1 (6.7)	0
Fentanyl + clonidine	0	1 (6.7)	0	0
Hydromorphone + bupivacaine	0	0	1 (6.7)	0
Hydromorphone + clonidine	1 (6.7)	0	0	0
Morphine + baclofen	0	0	1 (6.7)	0
Morphine + bupivacaine	1 (6.7)	0	0	2 (13.3)
Morphine + clonidine	0	1 (6.7)	0	0
Total, n (%)	**3 (20.0)**	**4 (26.7)**	**6 (40.0)**	**2 (13.3)**

a 11-point scale, from 0 (no pain) to 10 (worst pain imaginable).

in intrathecal opioid doses, intrathecal adjuvant drug doses, or systemic opioid use during ziconotide treatment, improved pain scores appeared to be associated with the addition of ziconotide to existing intrathecal regimens. However, 40.0% of patients experienced no change in pain and 13.3% of patients experienced a worsening of pain after the addition of intrathecal ziconotide.

When combination intrathecal therapy is used, it is important to consider drug stability because it can affect the frequency of pump refills. Studies have demonstrated that the stability of ziconotide can be compromised by the presence of other intrathecal agents, such as opioids (22-24). However, these effects appear to depend on the opioid concentration used. For example, ziconotide maintained 90% of its original concentration (90% stability) for 8 days when mixed with 35 mg/mL morphine and for 19 days when mixed with 20 mg/mL morphine (22,24). Studies to investigate the influence of ziconotide stability on the effectiveness of ziconotide combination therapy are required.

In our clinic, pump refill intervals are typically short when titrating a new intrathecal regimen. Because all of the patients in the current study had ziconotide added to their intrathecal regimens, pumps were refilled relatively frequently (mean, 26.2 days). However, once dosages are stabilized, efforts are made to maximize the length of time between refills.

Overall, combination intrathecal ziconotide and opioid therapy was safe and well tolerated in this patient population. The use of multiple drugs with different mechanisms of action may be an effective treatment option for patients who experience inadequate analgesia with intrathecal monotherapy treatment. Controlled trials to investigate the long-term safety and effectiveness of combination intrathecal ziconotide and opioid therapy are warranted.

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