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Focused Review

Considerations and Methodology for Trialing Ziconotide

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Background: Before long-term intrathecal analgesic therapy is initiated, patients often undergo a spinal analgesia trial. Ziconotide is a nonopioid intrathecal analgesic used to manage severe chronic pain, and a variety of methods have been used to trial ziconotide.

Objectives: The purpose of this review is to compare and discuss the different methods of ziconotide trialing.

Methods: Various databases (i.e., PubMed, Excerpta Medica, Cumulative Index to Nursing and Allied Health Literature, Biological Abstracts, Cochrane Database of Systematic Reviews, EMBASE, International Pharmaceutical Abstracts, and Google Scholar) and association meeting abstracts were searched with the use of the terms ziconotide, Prialt, trial, and trialing. In addition, a search was conducted for abstracts/posters presented at a variety of association meetings.

Results: Nine sources, including one expert opinion piece, were identified. Three methods of ziconotide trialing were discovered: continuous infusion, limited-duration infusion, and bolus injection. Results indicate that patients often achieve analgesia during trialing, regardless of the trialing method. Adverse events reported during ziconotide trialing studies were similar to those reported during ziconotide clinical trials. Preliminary evidence suggests that both effectiveness and safety may be dose-related. In 3 studies the value of ziconotide trialing in predicting long-term patient response to ziconotide therapy was investigated; however, the results were preliminary. The expert opinion piece from 2008 recommended trialing ziconotide via continuous infusion, using a starting dose of 1.2 mcg/d and dose increases of 1.2 mcg/d every 12 to 24 hours, for up to 3 days; the trial may be extended in some cases.

Limitations: Given the small samples size and lack of controlled ziconotide trialing studies, it is currently not possible to determine the relative safety and effectiveness of different methods of ziconotide trialing, nor is it possible to determine if trialing is predictive of patient response to long-term ziconotide therapy.

Conclusions: All 3 methods of ziconotide trialing appear to be viable options, and no method can be considered superior on the basis of the evidence presented in this review. Controlled studies comparing ziconotide trialing methods may be warranted.

Key words: Ziconotide, trialing, trial, review, intrathecal, chronic pain, Prialt, analgesic

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Intrathecal (IT) therapy is an important treatment option for patients with chronic pain who experience inadequate analgesia with other treatments (1,2). Compared to systemic analgesics, IT therapy has been associated with greater pain relief with lower doses of drug(s) and with a lower incidence of adverse events (AEs) (2,3).

Long-term IT therapy (e.g., > 3 months) generally involves the implantation of a permanent drug delivery system (pump and catheter). To optimize patient outcomes and improve costeffectiveness, a preliminary trial may be performed to assess patient response to spinal analgesia before pump implantation. Moreover, some insurance companies and government payers (e.g., Medicare) require specific trialing criteria or evidence of a successful trial (e.g., adequate pain relief, minimal side effects) before a patient qualifies for long-term IT therapy coverage (4).

There are numerous protocols that may be used for trialing spinal analgesia; these protocols differ in the mode of drug delivery (e.g., bolus injection, continuous infusion), site of administration (i.e., IT, epidural), and setting (i.e., inpatient, outpatient) (5). However, on the basis of available peer-reviewed literature, no trialing protocol is considered superior. The choice of trialing protocol is ultimately determined by each physician's standard of care (6).

Ziconotide (PRIALT®, ziconotide intrathecal infusion, Elan Pharmaceuticals, Inc., 800 Gateway Boulevard, South San Francisco, CA 94080) is a nonopioid IT analgesic indicated for the management of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine (7). Ziconotide is approved by the US Food and Drug Administration for monotherapy use only (7); the safety and efficacy of ziconotide in combination with other IT drugs have not been assessed in double-blind, placebo-controlled trials, and combination therapy is not recommended in the ziconotide prescribing information (7). Ziconotide is approved for use in SynchroMed® (Medtronic, 710 Medtronic Parkway, Minneapolis, MN 55432) or CADD-Micro (Sims Deltec, 1265 Grey Fox Rd, St. Paul, MN 55112) infusion pumps only (7). In animal studies, ziconotide was shown to selectively block N-type calcium channels in neurons of the dorsal horn of the spinal cord, thus preventing pain signals from reaching the brain (8); however, the mechanism of action of ziconotide has not been demonstrated in humans (7).

The safety and efficacy of ziconotide were investigated in 3 double-blind, placebo-controlled clinical trials; in none of these 3 studies were patients trialed on ziconotide before ziconotide therapy was initiated (9-11). In one study (9), starting patients at a low dose and slowly titrating the dose upward resulted in lower rates of serious AEs and lower rates of patient discontinuation due to AEs than were seen in 2 studies that started patients at higher doses and used faster rates of titration (10,11). On the other hand, effectiveness was more pronounced in the 2 studies that used higher starting doses and faster rates of titration (10,11) than it was in the study that used a low starting dose and a slow rate of titration (9).

For long-term ziconotide therapy, the current recommended approach is to start at a low dose and slowly titrate it upward (12). However, an effective trial of ziconotide must balance the improved effectiveness seen with the use of a high starting dose and fast titration against the improved safety seen with the use of a low starting dose and slow titration. Although a variety of ziconotide trialing procedures have been investigated (13-20), to date, the outcomes of those studies have not been reviewed.

Methods

Objectives

The purpose of the current paper is to summarize studies of ziconotide trialing procedures and to compare the different methods of ziconotide trialing.

Search Strategy

A search was conducted of the literature published from January 1995 through December 2008. The databases searched were PubMed, Excerpta Medica, Cumulative Index to Nursing and Allied Health Literature, Biological Abstracts, Cochrane Database of Systematic Reviews, EMBASE, and International Pharmaceutical Abstracts; the search terms were ziconotide, Prialt, trial, and trialing. Additionally, Google Scholar was used to search for articles in non-indexed journals, with the use of the same search terms. Because there are a limited number of published articles describing studies of ziconotide trialing, efforts were made to gather all data on the subject, regardless of source or level of evidence. A search was also conducted for association meetings that included abstracts/posters that related to IT therapy; only those sources that investigated ziconotide trialing were included in this review.

Data Extraction

Information on study design (e.g., open-label, case study), method of administration (e.g., bolus injection, continuous infusion), ziconotide doses, concomitant IT drugs, study duration, duration of treatment, pain condition(s), number of patients studied, pain outcome measures and results, and AEs were extracted from each publication, unless otherwise noted. Serious AEs and the resolution of AEs were detailed if they were described in the original report.

Results

Six association meetings were identified (years based on the availability of abstracts/posters as of January 27, 2009): North American Neuromodulation Society (2006 – 2008), American Academy of Pain Medicine (2001 – 2008), American Society of Anesthesiologists (2000 – 2008), American Society of Regional Anesthesia (2001 – 2008), American Pain Society (2003 – 2008), and International Association for the Study of Pain (2007 – 2008).

Eight published clinical reports, abstracts, or posters were identified (13-20). Studies and individual cases were categorized by the type of trial into 3 groups: continuous infusion trials, limited-duration infusion trials, and bolus trials. In addition, one expert opinion piece regarding the trialing of ziconotide was identified (6).

Continuous Infusion Trials

Three published reports that describe continuous infusion trialing studies were identified. One was an open-label study (18), one was a retrospective chart review (17), and one was a case report (20).

Continuous Infusion Trials: Open-label Investigation With External Pumps (Table 1) (18)

In this multicenter study, ziconotide was initiated at a dose of 2.4 mcg/d and titrated upward over the course of one to 4 weeks; doses were increased in increments of ≤ 2.4 mcg/d (up to 3 times per week) until meaningful analgesia or the maximum dose (21.6 mcg/d; this dose was higher than the maximum recommended dose in the ziconotide prescribing information [19.2 mcg/d]) (7) was achieved, or until intolerable AEs occurred. Effectiveness was assessed by Visual Analog Scale of Pain Intensity (VASPI) scores, the Categorical Pain Relief Scale (CPRS), and the Clinical Global Impression (CGI) scale (2 scales on which satisfaction with therapy and overall pain control were assessed).

A total of 71 patients with severe chronic malignant (n = 2) or nonmalignant (n = 69) pain were enrolled (39 men, 32 women; mean age, 52.8 years). Common pain types were neuropathic (70.4%), mixed (54.9%), nociceptive (40.8%), and degenerative (36.6%; patients could have been included in more than one pain clas-

Table 1. *Ziconotide Continuous Infusion Trialing: Summary of Data.*

Reference	Type of Study	N	Ziconotide Doses	Efficacy Results	Safety Results
Ver Donck et al (18)[a]	Open-label	71	Mean initial dose, 2.3 mcg/d; mean doses ranged from 3.4 to 4.1 mcg/d for the remainder of the study	• Median improvement from baseline in VASPI score ranged from 11.0% to 32.6% during the study	• Common AEs[b] were dizziness, nausea, asthenia, vertigo, and headache • SAEs occurred in 26.8% of patients; only one SAE was considered ziconotide related (asthenia/leg weakness)
Ting et al (17)[c]	Retrospective chart review	7	Initial dose, 1.2 or 2.4 mcg/d; mean maximum dose,[d] 2.5 or 5.6 mcg/d	• Adequate analgesia[e] was achieved by 71.4% of patients	• The AEs of post-dural puncture headache (n = 3), catheter dislodgment (n = 2), and deep vein thrombosis (n = 1) were reported
Wermeling & Berger (20)[f]	Case report	1	0.3 – 100.0 ng/kg per hour	• Substantial analgesia: VASPI score < 20 mm, achieved on Day 5	• The AEs of confusion, double vision, memory impairment, sedation, and slurred speech were reported; all AEs resolved after temporary (24-hour) discontinuation of ziconotide

Abbreviations: VASPI, Visual Analog Scale of Pain Intensity; AE, adverse event; SAE, serious adverse event.
a The study was sponsored by Elan Pharmaceuticals, Inc.
b AEs that occurred in > 5.0% of patients.
c This investigator-initiated study was supported by Elan Pharmaceuticals, Inc., by an educational grant to M. D. Anderson Cancer Center.
d Mean final doses for the groups receiving initial ziconotide doses of 1.2 or 2.4 mcg/d, respectively.
e Adequate analgesia was defined as a decrease in Visual Analog Scale score of ≥ 3 points or a > 50% self-reported improvement in pain relief.
f The authors of the study have conducted clinical research that was sponsored by Elan Pharmaceuticals, Inc.

sification). Mean ziconotide doses were 2.3 mcg/d at initiation, 3.4 mcg/d at Week 1, and 4.0 to 4.1 mcg/d for the remainder of the study. From baseline (before ziconotide exposure) to Weeks 1, 2, 3, and 4, VASPI scores significantly ($p \leq 0.005$) improved by a median of 11.0% (n = 69), 32.6% (n = 59), 31.0% (n = 48), and 23.5% (n = 23), respectively. At the termination visit, 52.2% of patients reported moderate to complete pain relief on the CPRS, 53.6% of patients reported good to excellent pain control on the CGI scale, and 62.3% of patients reported they were at least somewhat satisfied with ziconotide therapy on the CGI scale.

During the trial, the most common (experienced by > 5% of patients) ziconotide-related AEs were dizziness, nausea, asthenia, vertigo, and headache. Although serious AEs were reported by 19 patients (26.8%), only one of these AEs (asthenia/leg weakness) was considered to be related to ziconotide. Five patients (7.0%) developed meningitis during the trial; however, none of the cases were considered to be related to ziconotide therapy. Four of the 5 cases resolved within 10 days, and none of the cases were ongoing at study completion. In all instances, meningitis occurred after > 2 weeks of treatment with an external pump.

Continuous Infusion Trials: Retrospective Chart Review (Table 1) (17)

In this retrospective chart review, patient response to therapy was evaluated on the basis of achieving adequate analgesia, defined as a decrease from baseline Visual Analog Scale (VAS) pain score (an 11-point scale, with higher scores indicating worse pain) of ≥ 3 points or a > 50% improvement in self-reported pain relief.

Seven patients with chronic malignant (n = 1) or nonmalignant (n = 6) pain were identified and included in the study. Patients were divided into 2 groups on the basis of their starting ziconotide dose (1.2 or 2.4 mcg/d).

The first group consisted of 4 patients who started ziconotide at a dose of 1.2 mcg/d (2 men, 2 women; mean age, 52.8 years), including one patient who was trialed on combination ziconotide and bupivacaine. Two patients had postlaminectomy syndrome, one had postthoracotomy pain, and one had central thalamic stroke pain. Among these patients, the mean trial duration was 14.5 days, and the mean maximum ziconotide dose was 2.5 mcg/d. All 4 patients achieved adequate analgesia. Patients reported the AEs of post-dural puncture headache (n = 2), catheter dislodgment (n = 1), and deep vein thrombosis (n = 1). Both post–dural puncture headaches resolved with an epidural blood patch; the patient who experienced catheter dislodgment reported adequate analgesia at the time of dislodgment, and the catheter was not replaced. None of the AEs were considered to be related to ziconotide.

The second group consisted of 3 patients who started ziconotide at a dose of 2.4 mcg/d (2 men, one woman; mean age, 68.3 years). One patient had breast cancer/postmastectomy pain, one had pudendal neuralgia, and one had central thalamic stroke pain. The mean trial duration was 18.3 days, and the mean maximum ziconotide dose was 5.6 mcg/d. Adequate analgesia was achieved by one patient. The AEs of post–dural puncture headache (n = 1) and catheter dislodgment (n = 1) were reported. The post–dural puncture headache resolved with an epidural blood patch, and the dislodged catheter was replaced; neither AE was considered to be ziconotide related.

On the basis of these limited results, the safety and effectiveness of ziconotide trialing did not appear to be dose dependent.

Continuous Infusion Trials: Case Report (Table 1) (20)

The patient was a 54-year-old man with refractory peripheral neuropathy secondary to AIDS. He was implanted with an IT catheter and fitted with an external pump. Before starting ziconotide therapy, his VASPI score was 67 mm. For the first 24 hours of the trial, the patient was administered ziconotide at a dose of 0.3 ng/kg per hour (approximately 0.5 mcg/d for a 70 kg patient). The ziconotide dose was titrated upward to 1.0, 3.0, 10.0, 30.0, and 100.0 ng/kg per hour (approximately 1.7, 5.0, 16.8, 50.4, and 168.0 mcg/d, respectively) on Days 2, 3, 4, 5, and 6, respectively. On Day 5, the patient reported a substantial improvement in analgesia (VASPI score, < 20 mm). On Day 6, the patient reported confusion, double vision, memory impairment, sedation, and slurred speech. To manage these AEs, the ziconotide dose was decreased to 40 ng/kg per hour (approximately 67.2 mcg/d) for 24 hours; however, the AEs persisted. Ziconotide treatment was discontinued for 24 hours, and the AEs subsided. Ziconotide infusion was reinitiated at a dose of 20 ng/kg per hour (approximately 33.6 mcg/d).

The patient was discharged from the hospital, and he continued to receive ziconotide via an external pump for approximately 6 months. However, the patient was diagnosed with meningitis, and ziconotide therapy was discontinued; the meningitis was not believed to have been associated with ziconotide therapy.

Limited-Duration Infusion Trials

Two relevant citations were identified that used limited-duration ziconotide infusion; one was an open-label study (19), and one was a case series (20).

Limited-Duration Infusion Trials: Open-label Study (Table 2) (19)

In this study, patients with chronic nonmalignant pain and average VASPI scores of ≥50 mm during the 3 days before study entry were assigned to receive 1-, 5-, 7.5-, or 10-mcg IT infusions of ziconotide via an external pump over the course of one hour; patients had the option to receive an additional trial of ziconotide after at least one week had elapsed. Before the trial, patients were weaned from all spinal drugs. Effectiveness was evaluated via VASPI scores and the CPRS, which were assessed before initiating ziconotide treatment and periodically during the 48 hours after the start of the trial. The pharmacokinetics of ziconotide were evaluated by blood and cerebrospinal fluid (CSF) samples, which were obtained before the start of the trial and at 2, 4, 6, 8, 12, and 24 hours after the start of the infusion.

A total of 22 patients (11 men, 11 women; age range, 31 – 65 years) with chronic neuropathic pain participated in the study. Two patients received 2 doses of ziconotide, for a total of 24 trials; 5 patients received the 1-mcg dose, 8 patients received the 5-mcg dose, 6 patients received the 7.5-mcg dose, and 5 patients received the 10-mcg dose.

The means of the maximum improvement from baseline in VASPI scores during the first 4 hours after the start of the infusion were 8.4 mm, 14.0 mm, 28.8 mm, and 16.2 mm for the 1-mcg, 5-mcg, 7.5-mcg, and 10-mcg dose groups, respectively. The means of the maximum improvement from baseline in the CPRS during the first 4 hours after the start of the infusion were 2.2, 1.8, 2.7, and 2.0 for the 1-mcg, 5-mcg, 7.5-mcg, and 10-mcg dose groups, respectively. On the basis of these and other effectiveness results, the authors concluded that analgesia was dose related. In addition, the area under the concentration-time curve for CSF ziconotide levels was significantly positively correlated ($P < 0.05$) with the results of several effectiveness parameters.

Two of the patients (40.0%) in the 1-mcg ziconotide dose group and all of the patients in the remaining groups experienced at least one AE during the study; however, most AEs were considered mild to moderate in severity. Although 4 patients experienced hypotension, there was no relationship between hypotension and plasma levels of ziconotide. Three severe AEs were reported (myasthenia, dizziness, and headache), all of which occurred in the 10-mcg ziconotide dose group. Both ziconotide dose and area under the concentration-time curve for CSF ziconotide levels were significantly positively correlated ($P < 0.05$) with an increased incidence of AEs in general.

Table 2. *Ziconotide Limited Duration Infusion Trialing: Summary of Data*[a]

Reference	Type of Study	N	Ziconotide Doses	Efficacy Results	Safety Results
Wermeling et al (19)[b]	Open-label	22	1, 5, 7.5, and 10 mcg	• Dose-related analgesia; CSF levels of ziconotide were significantly positively correlated ($P < 0.05$) with several indices of effectiveness	• AEs were reported by 40% of patients after the 1-mcg infusion and by 100% of patients in the remaining dose groups • 3 severe AEs were reported among patients who received 10-mcg doses (myasthenia, dizziness, and headache) • Dose and CSF levels of ziconotide were significantly positively correlated ($P < 0.05$) with the incidence of AEs
Wermeling and Berger (20)[c]	Case reports	2	5- or 10-mcg epidural infusion	• Substantial analgesia for ≥ 7 hours; first patient, VASPI score of 0 mm (during hours 1-3 and 5-20); second patient, VASPI score < 20 mm (during first 7 hours)	• Both patients reported the AEs of headache and somnolence • The AEs of light headedness, pruritus, nausea, and hypotension were reported by one or the other patient • All AEs resolved within several hours

Abbreviations: CSF, cerebrospinal fluid; AE, adverse event; VASPI, Visual Analog Scale of Pain Intensity.
a Ziconotide was administered intrathecally unless otherwise noted.
b The study was sponsored by Elan Pharmaceuticals, Inc.
c The authors of the study have conducted clinical research that was sponsored by Elan Pharmaceuticals, Inc.

Limited-Duration Epidural Infusion Trials: Case Series (Table 2) (20)

The safety and effectiveness of limited-duration ziconotide epidural trials were reported in 2 case reports. The first patient was a 47-year-old woman with right sacroiliac joint dysfunction and complex regional pain syndrome. Because lumbar sympathetic blocks provided only moderate relief, she chose to receive a trial of ziconotide. Over the course of one hour, 10-mcg ziconotide was delivered via an epidural catheter. Results from VASPI scores and the CPRS indicated that ziconotide provided dramatic analgesia that lasted > 20 hours; at some time points during the trial, her VASPI score was 0 mm (hours one – 3 and 5 – 20; baseline VASPI score, 68 mm), and her CPRS was 5 (Hours 1-3 and 5-12). The patient experienced AEs of light-headedness, headache, and somnolence that began 2 hours after ziconotide administration; these AEs were considered mild in nature, and they resolved several hours after the trial.

The second case was a 47-year-old woman with lumbar degenerative disc disease, facet syndrome, lumbar radiculitis, sciatica, and myofascial pain syndrome. Systemic analgesics provided limited pain relief (VASPI score, 85 mm), and the patient was administered 5 mcg ziconotide via an epidural catheter over the course of one hour. She experienced substantial analgesia during the trial; VASPI scores assessed during the first 7 hours after the infusion were generally < 20 mm, and she most often reported a CPRS score of 4 during the first 12 hours after the infusion. The patient experienced greater mobility and was able to discontinue systemic analgesics for > 24 hours. Although the patient exhibited a decrease in blood pressure that lasted 16 hours, she did not experience any orthostatic symptoms. The patient reported the mild AEs of somnolence, pruritus, nausea, and headache; these AEs resolved within 10 hours.

Bolus Trials

One of each of the following types of ziconotide bolus injection investigations was identified: a small double-blind, placebo-controlled trial (16), an open-label study (14), a single-center trial (15), and a retrospective chart review (13). The value of ziconotide bolus injections in predicting patient response to long-term therapy was assessed in the last 3 bolus injection studies (13-15).

Bolus Trials: Double-blind, Placebo-Controlled Trial (Table 3) (16)

Each patient with severe chronic pain in this study was administered up to 4 IT ziconotide injections (placebo [0 mcg], 2, 4, and 8 mcg in a randomized sequence) over a one-month period. VASPI scores were assessed before each injection (baseline) and each hour after the injection for 6 hours.

Data were obtained from 6 patients, who received a total of 20 injections (4 injections of placebo and of 4 mcg ziconotide, 6 injections of 2 mcg ziconotide and of 8 mcg ziconotide). Pain types were post–lumbar laminectomy syndrome (n = 4), erythromelalgia (n = 1), and spinal cord injury (n = 1). The proportion of patients who reported > 50% reduction from baseline in VASPI score was 0% after the placebo injection, 17% after the 2-mcg ziconotide injection, 25% after the 4-mcg ziconotide injection, and 50% after the 8-mcg ziconotide injection. The proportion of patients who reported > 30% reduction from baseline in VASPI score was 25% after the placebo injection, 17% after the 2-mcg ziconotide injection, 50% after the 4-mcg ziconotide injection, and 67% after the 8-mcg ziconotide injection; these proportions included those patients who achieved > 0% reduction in VASPI score. The proportion of patients who reported ≤ 30% reduction from baseline in VASPI score was 75% after the placebo injection, 83% after the 2-mcg ziconotide injection, 50% after the 4-mcg ziconotide injection, and 33% after the 8-mcg ziconotide injection. Two patients (33%) reported nausea and vomiting and ataxia after the 8-mcg ziconotide injection. Patients reported mild nausea and/or dizziness after 6 of the 16 (38%) ziconotide injections and after one of the 4 (25%) placebo injections.

Bolus Trials: Open-label Study (Table 3) (14)

The predictive value of IT bolus trialing for the effectiveness of long-term ziconotide therapy was assessed in this ongoing study. Patients in this study had chronic nonmalignant pain that was refractory to systemic and/or IT opioid therapy. A 1-mcg IT injection of ziconotide was administered to each patient; pain was rated on a VAS before (baseline), one hour, and 24 hours after the injection. In addition, one and 24 hours after injection, patients were administered the Patient Satisfaction Questionnaire (PSQ), on which patients indicated whether they strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree that they were satisfied with the trial of ziconotide. If effectiveness (a ≥ 50% improvement in pain score from baseline) was not achieved and no serious AEs were reported, patients had the option to receive up to 2 additional ziconotide injections (3 and 5 mcg). Patients who experi-

Table 3. *Ziconotide Bolus Trialing: Summary of Data.*

Reference	Type of Study	N	Ziconotide Doses	Efficacy Results	Safety Results
Rosenblum (16)[a]	Randomized, double-blind, placebo-controlled	6	Placebo (0 mcg), 2, 4, and 8 mcg	• Dose-related analgesia	• Mild nausea and/or dizziness were reported after 38% of ziconotide injections and after 25% of placebo injections • 33% of patients reported nausea and vomiting and ataxia after the 8-mcg injection
Grigsby and McGlothlen (14)[a]	Ongoing, single-center, open-label	42	1 mcg, with the possibility of up to 2 additional doses (3 and 5 mcg)	• 18.5% (n = 27) of patients achieved effectiveness[b] after the 1-mcg injection	• 3 of 27 patients (11.1%) experienced AEs (nausea with or without vomiting); all AEs resolved spontaneously
Okano et al (15)	Single-center	11	1.2, 2.4, and 5 mcg	• 72.7% of patients reported a >50% improvement in pain relief	• 3 patients (27.3%) experienced SAEs (urinary retention, hallucination, and motor weakness, respectively)
Baumgartl (13)[a]	Retrospective chart review	4	5, 40, and 50 mcg	• 75% of patients reported pain score reductions of 2-5 points (on a 10-point scale)	• one patient reported dysphoria; one patient reported nausea and dizziness

Abbreviations: AE, adverse event; SAE, serious adverse event.
a An investigator initiated trial that was sponsored by Elan Pharmaceuticals, Inc.
b A ≥50% improvement over baseline in pain score.

enced effectiveness at any time within 24 hours and/or who were satisfied with their trial were administered continuous IT ziconotide therapy (added to their existing IT regimen, if applicable). Pain was assessed on a VAS at 2 weeks and at one, 3, 6, and 12 months of continuous infusion.

At last assessment, 42 patients had enrolled in the study. Common pain types were failed back surgery syndrome (45.2%), degenerative disk disease (31.0%), and low back pain (16.7%). Twenty-seven patients received a 1-mcg ziconotide injection; 5 of these patients (18.5%) experienced effectiveness, and the majority of patients either agreed or strongly agreed on the PSQ that ziconotide provided satisfactory pain relief at both one hour (55.6%; n = 27) and 24 hours (58.3%; n = 24) after the injection. One additional patient experienced partial effectiveness (relief of her back pain but not her hip pain) and proceeded to the 3-mcg trial. Eight patients received a 3-mcg ziconotide injection; 3 patients (37.5%) experienced effectiveness and many patients either agreed or strongly agreed that ziconotide provided satisfactory pain relief at both one hour (42.9%; n = 7) and 24 hours (42.9%; n = 7) after the injection. The 2 patients who received a 5-mcg injection did not experience effectiveness. Nausea and/or vomiting was reported by 2 patients during the 1-mcg trial and by one patient during the 3-mcg trial; these AEs resolved spontaneously in all patients.

Sixteen patients received continuous ziconotide therapy (mean dose at last assessment, 1.19 mcg/d; range, 0.60 – 5.00 mcg/d), and 2 patients were scheduled to begin continuous ziconotide infusion in this ongoing trial. Improvements in pain scores from baseline (range, 12.5%-100%) were experienced by 4 of 15 patients (26.7%) after 2 weeks of continuous ziconotide infusion, 5 of 12 patients (41.7%) after one month, 5 of 7 patients (71.4%) after 3 months, and 2 of 5 patients (40.0%) after 6 months. On the PSQ, the number of patients who agreed or strongly agreed that ziconotide provided satisfactory pain relief during continuous infusion were 8 of 15 patients (53.3%) after 2 weeks, 6 of 12 patients (50.0%) after one month, 7 of 7 patients (100%) after 3 months, and 4 of 5 patients (80.0%) after 6 months. Pain scores were either unchanged or had worsened for the remaining patients at each time point. Continuous infusion was discontinued in 2 patients; one patient discontinued because of cognitive changes and the other patient discontinued for personal reasons.

Bolus Trials: Single-Center Study (Table 3) (15)

The value of ziconotide bolus trialing in predicting long-term patient response to ziconotide was also investigated in this study. Eleven patients with existing IT pumps received a 1.2-mcg (n = 4), 2.4-mcg (n = 5), or 5.0-mcg (n = 2) ziconotide bolus injection. Patients were evaluated 2 weeks after the injection. Serious AEs were reported by 3 of 11 patients (27.3%; urinary retention,

hallucination, and motor weakness, respectively); both patients who received a 5-mcg injection reported serious AEs (urinary retention and motor weakness, respectively). Eight of 11 patients (72.7%) experienced > 50% improvements in pain relief after the ziconotide injection; these patients had ziconotide added to their existing IT regimens. Seven of the 8 patients (87.5%) who received continuous ziconotide infusion reported improved analgesia after 6 months of ziconotide treatment.

Bolus Trials: Retrospective Chart Review (Table 3) (13)

The predictive value of high-dose IT ziconotide bolus trialing was evaluated in this chart review. Four patients who received IT bolus administration of ziconotide were identified (patients may have received more than one injection); 2 patients received a 5-mcg injection, 2 patients received a 40-mcg injection, and 2 patients received a 50-mcg injection. After trialing, 3 patients (75%) reported a pain reduction of 2 to 5 points (on a 10-point scale); pain relief first occurred between the third and fourth hour after injection and lasted for approximately 3 to 6 hours. One patient reported the AE of short-term dysphoria after receiving a 5-mcg injection, and one patient reported the AEs of nausea and dizziness after receiving a 50-mcg injection. After trialing, 3 patients were administered continuous IT ziconotide via an external pump. During continuous infusion, one patient who had experienced analgesia during trialing experienced similar analgesia during infusion, one patient who had experienced no analgesia during trialing experienced no analgesia during infusion, and one patient who had experienced analgesia during trialing experienced no analgesia during infusion.

Expert Opinion

A group of physicians familiar with ziconotide treatment published one potential protocol for trialing ziconotide (6). Continuous IT ziconotide infusion was the recommended means of trialing, and the suggested dosing schedule was 1.2 mcg/d at initiation with dose increases of 1.2 mcg/d every 12 to 24 hours, over the course of 3 days. The authors stated that the trial may be ended early if adequate analgesia is achieved before the end of 3 days and that the trial may be extended if adequate analgesia is not achieved after 3 days and AEs are absent or tolerable. If intolerable AEs occur, it was recommended that the trial be terminated immediately. Although the guidelines indicated that trialing may be performed on an inpatient or outpatient basis, it was suggested that patients be hospitalized for at least 24 hours and closely monitored for life-threatening AEs or complications.

The rate of upward titration recommended for ziconotide trialing in these guidelines is greater than the rate of upward titration recommended for beginning long-term ziconotide therapy (12); therefore, the severity and frequency of AEs is likely to be higher during trialing than during long-term therapy. The guidelines stressed that administration of long-term ziconotide therapy should not start at the final dose achieved during the trial; long-term therapy should be reinitiated at a low dose (0.5 – 2.4 mcg/d), and dose increases should occur ≤ one time per week.

Discussion

Most of the studies reviewed were not randomized clinical trials. Although reviewing small nonrandomized trials (some of which are not published) is unconventional, the authors felt that identification of all existing literature in this therapeutic area was important.

Physician preferences for trialing spinal analgesia appear to have changed over the past decade. One report from 1996 indicated that only 6.4% of patients were trialed with continuous IT infusion (21); however, 45% of respondents to a 2005 physician survey preferred trialing by continuous IT infusion (5). Although most pain clinicians are aware of the value of IT analgesic trials, controlled studies to compare the safety and effectiveness of different trialing methods have not yet been performed. Instead, clinicians must rely on empiric or consensus-driven algorithms when determining trialing protocols. In one published algorithm, IT bolus injections are the suggested means of trialing in patients with refractory cancer pain with life expectancies > 3 months; however, continuous IT infusion trials are recommended for patients who experience inadequate analgesia with a bolus injection trial, patients who have a severe incidental pain syndrome, or patients with neuropathic pain (22). Although long-term IT therapy is more closely simulated by continuous IT infusion trialing than by bolus trialing, bolus trialing is simpler to perform and is less expensive than is continuous IT infusion trialing (2). Unlike continuous infusion trials, a bolus injection trial may provide an inadequate time frame to assess potential AEs; however, the likelihood of infectious complications is greater with continuous infusion trials than with bolus trials. Trialing ziconotide via continuous IT infusion is the method recommended

in one expert opinion piece (6).

The dose of ziconotide administered during a trial may be related to the effectiveness of that trial. Results from a limited-duration infusion study and a bolus injection study reveal that patients who received higher doses of ziconotide often experienced greater pain relief than did patients who received lower doses of ziconotide (16,19). Results from the limited-duration infusion study also indicated that several effectiveness parameters were significantly positively correlated ($P < 0.05$) with the area under the concentration-time curve for CSF ziconotide levels. However, results from a small (N = 7) retrospective study of continuous ziconotide infusion trials indicate that effectiveness is not dose-related (17).

In addition to potentially being related to effectiveness, the dose of ziconotide administered to a patient during trialing may also be related to the incidence of AEs. Results from the largest (N = 22) ziconotide trialing study that compared the effects of different ziconotide doses revealed that both higher doses of ziconotide and higher CSF levels of ziconotide were significantly positively correlated ($P < 0.05$) with an increased incidence of AEs (19). In that study, serious AEs (myasthenia, dizziness, headache) were reported by only those patients who received the highest dose of ziconotide (10 mcg). However, results from a retrospective study of continuous ziconotide infusion trials suggest that safety is not dose related (17). In the remaining trialing studies, the relationship between ziconotide dose and the incidence of AEs was either not reported or difficult to ascertain because of the small sample sizes. In general, the AEs reported in ziconotide trialing studies were similar to those reported in ziconotide clinical trials (9-11).

Meningitis is a potential risk of continuous IT infusion trialing via an external pump. For example, 37 of the 40 (92.5%) cases of meningitis that occurred in ziconotide-treated patients during clinical trials were in patients with external drug pumps (7). In the open-label continuous infusion trialing study of ziconotide, meningitis occurred in 7.0% of patients (18). In that study, all cases of meningitis occurred after > 2 weeks of IT infusion, suggesting that limiting the length of a continuous infusion trial may likely reduce the risk of meningitis. In an expert opinion piece on ziconotide trialing, the recommended length of a continuous IT ziconotide infusion trial was 3 days (6). Clinicians may choose to trial patients with known risk factors for the development of meningitis (e.g., diabetes, severe rheumatologic diseases, malignancies, or potentially altered immune states) (23-25) with bolus injections instead of continuous infusion, or to use continuous infusion but limit the duration of each trial to a few days.

To date, the superiority of one particular trialing method over another in predicting long-term patient response to spinal analgesia has not been demonstrated. In a prospective, randomized investigation of morphine trialing, it was discovered that bolus injections were no more predictive of long-term patient response than were continuous epidural infusion trials (26). The predictive value of ziconotide trialing was investigated in 3 studies; bolus injections of ziconotide were used in all of these investigations (13-15). In 2 studies, patients who experienced analgesia and/or were satisfied with their trial also often reported pain relief during continuous infusion (14,15). Results from the other study were mixed; however, it had a very small sample size (n = 4) (13). In all 3 studies, generally only those patients who experienced analgesia during trialing went on to receive continuous ziconotide infusion, indicating a selection bias. Controlled studies are necessary to determine which method of ziconotide trialing is most predictive of patient response to long-term ziconotide therapy.

Trialing ziconotide via the epidural route was associated with analgesia in 2 published case reports (20). However, ziconotide is a large, hydrophilic molecule, and transport from the epidural to the IT space is likely inhibited (6); the molecular weight of ziconotide (2639 Daltons [Da]) is greater than that of small-molecule drugs that may be delivered epidurally (e.g., morphine [285 Da], clonidine [230 Da]) (7,27,28). Furthermore, ziconotide is approved for IT administration only (7).

A 2009 survey of health care professionals who use IT therapy in their practices revealed that the majority of practitioners (64.0%) indicated that between 26% and 50% of their pain management patients are insured by a government payer such as Medicare (29). Numerous third-party payers, including Medicare, mandate a successful neuraxial analgesic trial (e.g., improved analgesia, tolerable AEs) before an implantable infusion pump will be reimbursed. The Medicare guidelines require that, for a patient who requires spinally infused opioids for the treatment of chronic pain, an initial trial "must be undertaken with a temporary intrathecal/epidural catheter to substantiate adequately acceptable pain relief and degree of side effects (including effects on the activities of daily living) and patient acceptance" (4). Notably, clinical experience with IT opioids was limited when this requirement was written; revision of the

requirement on the basis of currently available data may be warranted. Although the method of trialing is not specified by Medicare, it is possible that regional carriers have distinct trialing requirements. Therefore, the need exists for examples of different trialing procedures to be detailed in the published literature.

Although literature on this topic is scant and mainly consists of small nonrandomized trials, after careful review of the available data and their own clinical experience, the authors recommend continuous IT infusion trials of ziconotide be used when feasible. However, the authors also recognize the need for controlled studies to further investigate other trialing procedures.

Conclusion

Preliminary reports suggest that continuous ziconotide trialing, in addition to being the method recommended by an expert group, generally produced analgesia (17,18,20). However, analgesia is also associated with limited-duration infusion trialing (19,20) and bolus trialing (13-16). Thus, all 3 methods may be viable means of trialing ziconotide. Given the small samples sizes and lack of controlled studies, it is currently not possible to determine the relative safety and effectiveness of these trialing methods, nor is it possible to determine if trialing predicts patient response to long-term ziconotide therapy. Controlled studies that compare different ziconotide trialing procedures may be warranted.

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