Intrathecal Ziconotide in the Treatment of Refractory Pain in Patients With Cancer or AIDS

A Randomized Controlled Trial

Peter S. Staats, MD
Thomas Yearwood, MD, PhD
Steven G. Charapata, MD
Robert W. Presley, MD
Mark S. Wallace, MD
Michael Byas-Smith, MD
Robert Fisher, MD
David A. Bryce, MD
Eugene A. Mangieri, MD
Robert R. Luther, MD
Martha Mayo, PharmD
Dawn McGuire, MD
David Ellis, MD, PhD

Context Ziconotide (formerly SNX-111) selectively blocks N-type voltage-sensitive calcium channels and may be effective in patients with pain that is refractory to opioid therapy or those with intolerable opioid-related adverse effects.

Objective To assess the safety and efficacy of intrathecal ziconotide in patients with pain that is refractory to conventional treatment.

Design, Setting, and Patients Double-blind, placebo-controlled, randomized trial conducted from March 12, 1996, to July 11, 1998, at 32 study centers in the United States, Australia, and the Netherlands. Patients were 111 individuals ages 24 to 85 years with cancer or AIDS and a mean Visual Analog Scale of Pain Intensity (VASPI) score of 50 mm or greater. Patients were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment.

Interventions Intrathecal ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of nonresponders to the opposite treatment group.

Main Outcome Measure Mean percentage change in VASPI score from baseline to the end of the initial titration period.

Results Of the evaluable population, 67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/d for the ziconotide group and 600 mg/d for the placebo group; $P=.63$, based on mean values), and 36 had used intrathecal morphine. Mean (SD) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group ($P=.18$). Mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($P<.001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group ($P<.001$). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo ($P=.001$).

Conclusion Intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS.

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Ziconotide (formerly SNX-111, Neurex Pharmaceuticals, Menlo Park, Calif) is the synthetic equivalent of ω-conopeptide MVIIA, a 25–amino-acid polybasic peptide present in the venom of *Conus magus*, a marine snail.[1] Ziconotide produces potent antinociceptive effects[2] by selectively binding to N-type voltage-sensitive calcium channels[3,4] on neuronal somata, dendrites, dendritic shafts, and axon terminals, thus blocking neurotransmission from primary nociceptive afferents.

Ziconotide is the first selective N-type voltage-sensitive calcium channel blocking agent to be tested in clinical trials. There is no evidence of tolerance to ziconotide[5] or of addictive behavior in animals (Elan Pharmaceuticals Inc, unpublished data), and the drug must be administered intrathecally to maximize antinociceptive effectiveness and minimize sympatholysis.[6]

Author Affiliations: Division of Pain Medicine, Johns Hopkins University School of Medicine, Baltimore, Md (Dr Staats); Integrated Spine Clinic, Daphne, Ala (Dr Yearwood); Pain Management Associates, Research Medical Center, Pain Institute, Kansas City, Mo (Dr Charapata); Pain Care Specialists, Colorado Springs, Colo (Dr Presley); Center for Pain and Palliative Medicine, University of California, San Diego, La Jolla (Dr Wallace); Department of Anesthesia, Emory University School of Medicine, Atlanta, Ga (Dr Byas-Smith); R. C. Goodman Institute for Pain Management, Sparks Regional Medical Center, Fort Smith, Ark (Dr Fisher); Marshfield Clinic, Marshfield, Wis (Dr Bryce); Anodyne Research Services, Northport, Ala (Dr Mangieri); Rhino Pias Consulting LLC, Reno, Nev (Dr Luther); Eunoe Inc, Redwood City, Calif (Drs Mayo and McGuire); Elan Pharmaceuticals Inc, San Diego, Calif (Dr Ellis).
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Corresponding Author and Reprints: Peter S. Staats, MD, Division of Pain Medicine, Johns Hopkins University School of Medicine, 550 N Broadway, Suite 301, Baltimore, MD 21205 (e-mail: pstaats@jhmi.edu).

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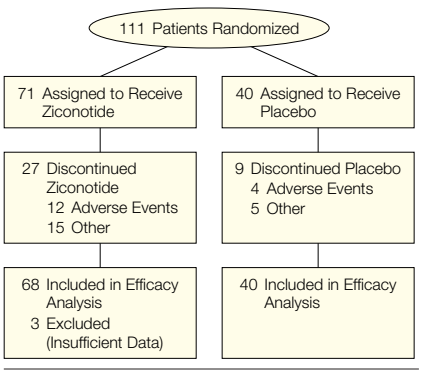
Figure 1. Study Flow



Many patients with cancer or AIDS do not receive satisfactory pain relief[7,8] from systemic administration of opioids and become potential candidates for intraspinal analgesia.[9-11] However, regardless of delivery route, concerns about addiction and abuse, and the potential for developing tolerance, adverse effects, and pain refractoriness limit the effectiveness of opioids.

In experimental studies of absorption, distribution, metabolism, and elimination, intrathecal ziconotide appeared and diminished rapidly in plasma and resulted in relatively little plasma protein binding. Intravenous ziconotide degraded in rat brain tissue in 2 to 24 hours, produced no detectable intermediates, and cleared quickly from both cerebrospinal fluid (CSF) and the circulatory system. This accelerated clearance rate likely means that the distribution of ziconotide throughout the CSF and its metabolism within the CSF are also rapid.[6]

Investigators demonstrated the antinociceptive effects of ziconotide in various animal models of acute and chronic pain (eg, formalin, hot-plate, and ligation).[12,13] Toxicology studies revealed no organ specificity, mutogenicity, or teratogenicity, even at higher doses than would be used in humans (Elan Pharmaceuticals Inc, unpublished data).

In clinical pharmacokinetic studies using high intravenous doses and low intrathecal doses, ziconotide exhibited a linear clearance from plasma and CSF, with plasma concentrations of ziconotide below the quantitation assay minimum of 0.039 ng/mL (Elan Pharmaceuticals Inc, unpublished data). The rate of CSF clearance of intrathecal ziconotide approximated the CSF turnover rate (mean elimination half-life of 4.6 hours).

An initial, open-label feasibility study evaluated 31 male patients with chronic pain states of diverse indications, including cancer, AIDS, spinal cord injury, thalamic pain, and brachial plexus avulsion.[14] None of the patients had received adequate pain control with opioid therapy, including, in many cases, intrathecal opioid therapy. Patients received a continuous infusion of ziconotide via an intrathecal catheter beginning at a dosage of 0.3 ng/kg per hour, which was titrated upward to the point of pain relief or intolerable adverse effects, with a maximum dosage of 300 ng/kg per hour. Of the 24 patients who completed the study, 19 experienced an average reduction of 43% in their Visual Analog Scale of Pain Intensity (VASPI) score. Fifteen patients were able to reduce their concomitant use of opioids by at least 50%.

Investigators have reported the following central nervous system adverse effects associated with the use of intrathecal ziconotide: dizziness, nystagmus, confusion, abnormal gait, somnolence, speech difficulties, amblyopia, ataxia, amnesia, and abnormal thought processes.[15] These effects diminished or resolved when the investigators reduced the infusion rate or ceased infusion. The patients who reported major adverse effects had been receiving 0.2 to 5.3 µg/h of intrathecal ziconotide.

Encouraged by this preliminary evidence of human analgesia, we conducted a randomized, double-blind, placebo-controlled trial to test the effectiveness of intrathecal ziconotide in treating refractory pain in patients with cancer or AIDS.

METHODS

Study Population

To be eligible, patients with cancer or AIDS from 32 centers in the United States, Australia, and the Netherlands needed to have a mean VASPI score of 50 mm or greater during the 3 days before enrollment, despite a regimen of systemic or intrathecal analgesics. The VASPI is a scale commonly used in assessments of pain therapy, in which patients rate their pain on a scale of 0 mm (no pain) to 100 mm (worst pain imaginable). We discontinued intrathecal medications in the patients with implanted pumps at least 3 days prior to study enrollment. According to accepted clinical practice, the investigators weaned patients from baseline intrathecal medications and maximized systemic and oral medications to control pain during this period.

Exclusion criteria included pregnancy, sepsis or inadequately treated infection, investigational drug use, or palliative surgical procedure(s) within the preceding 30 days; dementia; untreated affective disorders; nonpatent spinal canal; severe asthma, cardiac failure, or bradyarrhythmias; and neurocardiogenic syncope. Prior to enrolling patients, each study center obtained institutional review board/institutional ethics committee approval and obtained written informed consent from all patients.

Study Design

For this double-blind, placebo-controlled, randomized study, we used a central call-in system to randomly assign patients in a 2:1 ratio to receive ziconotide or placebo treatment, stratified within each center by cancer or AIDS diagnosis and by history of intrathecal morphine use. The study began with a screening phase and preinfusion evaluation (1-7 days). In patients without previously implanted pumps, we implanted an intrathecal catheter and used an external infusion system. Given the risk of infection with the use of external systems, we limited the total time frame for drug infusion to 2 weeks for all patients.

In the initial titration phase, participants received ziconotide or placebo for 5 days (for nonresponders, a discretionary additional day at any given dosage or increased dosage could be given).

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Responders received an additional 5 days of maintenance therapy while nonresponders crossed over to the opposite group for an additional 5 or 6 days. Ziconotide responders could enroll in a long-term, open-label study.

The protocol defined responders as patients with a 30% or greater decrease in mean VASPI score and no increase in concomitant opioid use or change in opioid type. The study protocol was consistent across all study centers.

Data Collection

Starting from screening and preinfusion visits and in 24-hour intervals, we calculated values for the VASPI, the 5-point Category Pain Relief Scale (CPRS), the Wisconsin Brief Pain Inventory (WBPI), the Karnofsky Performance Status Scale (KPSS), as well as mean percentage change in opioid use and response to treatment.

Drug Administration

Dosing of ziconotide (an aqueous isotonic solution of 100 µg/mL ziconotide free-base with L-methionine and sodium chloride as excipients) and placebo (identical vehicle) during the early stage of enrollment in the study was 5 ng/kg per hour. To minimize variability, we changed this dosage to 0.4 µg/h with incremental increases in titration every 12 hours to the maximum tolerated dosage of ziconotide. Based on safety evaluations of the first 48 enrolled participants, we decreased the starting dosage for 60 subsequent participants to 0.1 µg/h or less, with upward titrations once every 24 hours to the point of analgesic effect or to a discretionary maximum dosage of 2.4 µg/h. We adjusted concentrations as required by final daily doses and apparatus used. Patients could receive other systemic medications, including opioids, as clinically indicated, but not adjuvant intrathecal agents.

End Points and Measurements

The primary efficacy variable was mean percentage change in VASPI score from baseline (score immediately prior to infusion) to the end of the initial titration period (mean of the last 2 VASPI scores or of the last 3 VASPI scores if the first 2 scores differed by more than 15 mm). Responders had a 30% or greater decrease in VASPI scores, with no concomitant increase in opioid use or change in opioid class.

We also calculated the percentage change in the CPRS, the WBPI, and the KPSS; the change in opioid use; and the change in responder status from baseline to the end of the maintenance phase and of the crossover phase, as dictated prospectively by the protocol. We recorded adverse events, vital signs, and the results of cognitive assessments (trail-making and digit symbol tests), and clinical laboratory evaluations (blood chemistry, hematology, urinalysis, and electrocardiography). For the timed cognitive tests, we asked patients to draw a line between numbered circles or between numbered and lettered circles, or to decode a series of 9 simple symbols.

Masking

Study sponsors, principal investigators, and patients did not know group assignments during the trial. Only the pharmacists who prepared the study drugs knew each patient's status.

Statistical Analysis

The planned sample size was 70 evaluable patients receiving ziconotide (with

Table 1. Demographic and Baseline Characteristics of the Evaluable Sample

Characteristic	Initial Treatment Assignment, No (%)		*P* Value
	Ziconotide (n = 68)	Placebo (n = 40)	
Age, y			
Mean (SE)	55.3 (1.72)	56.6 (2.07)	.78
Median (range)	57.5 (24.0-81.0)	56.0 (33.0-85.0)	
Sex			
Women	34	20	.97
Men	34	20	
Race			
White	57 (83.8)	38 (95.0)	.09*
Black	8 (11.8)	1 (2.5)	
Hispanic	3 (4.4)	0	
Asian	0	1 (2.5)	
Diagnosis			
Cancer	59 (86.8)	36 (90.0)	.62
Breast	11	12	
Lung	13	5	
Colorectal	10	5	
Prostate	5	2	
Myelogenous/lymphatic	7	3	
Skin	3	2	
Other	10	7	
AIDS	9 (13.2)	4 (10.0)	
Currently receiving systemic analgesics	64 (94.1)	38 (95.0)	.85
Oral morphine equivalent, mg/d†			
Mean (SE)	6200 (3310)	4200 (1200)	.63
Median (range)	300 (0-201 800)	600 (0-30 000)	
Prior intrathecal morphine	22 (32.4)	14 (35.0)	.78
Pain responsive to intrathecal morphine‡	9 (40.9)	6 (42.9)	.91
KPSS§			
Mean (SE)	64.4 (1.92)	60.5 (2.41)	.33
Median (range)	70.0 (30.0-90.0)	60.0 (30.0-90.0)	

Abbreviation: KPSS, Karnofsky Performance Status Score.
*For white vs black, Hispanic, and Asian combined.
†Compared using analysis of variance; *P* value is based on mean values.
‡Percentages based on number of patients who received previous intrathecal morphine therapy (n = 22 for ziconotide; n = 14 for placebo).
§Scores on the KPSS range from 0 (dead) to 100 (normal, with no evidence of disease). Values reported are based on n = 62 for ziconotide and n = 38 for placebo.

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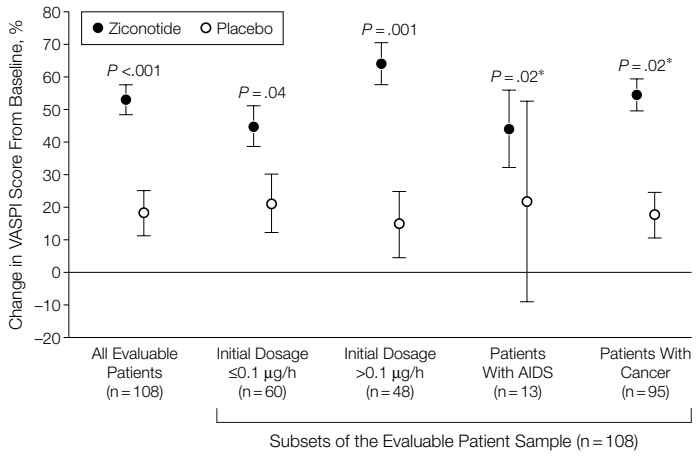
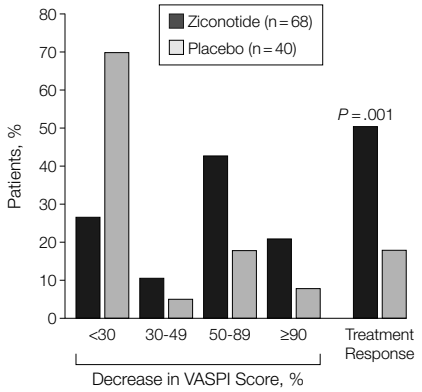
Figure 2. Reduction in Pain Intensity by Dosage and Diagnosis



VASPI indicates Visual Analog Scale of Pain Intensity. Error bars indicate SEM. *After adjustment for diagnosis.

Figure 3. Percentage of Patients With Various Degrees of Improvement in Pain Intensity and Those Meeting Criteria for Response to Treatment



VASPI indicates Visual Analog Scale of Pain Intensity. Response to treatment defined as a ≥30% decrease in VASPI scores, without a concomitant increase in opioid use or a change in opioid class.

complete VASPI data at the end of the initial titration period and no substantial violations of the protocol) and 35 evaluable patients receiving placebo. This sample size has a 96% statistical power at the .05 significance level to detect a greater than 30% change in VASPI scores in the 2 treatment groups. Statistical analyses were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC). We conducted 2-way analyses of variance of the mean percentage change in VASPI scores and KPSS scores, with treatment, previous use of intrathecal morphine (yes/no), and treatment × previous use of intrathecal morphine as interaction terms. We used the Cochran-Mantel-Haenszel test stratified by history of intrathecal opioid use to analyze differences in the CPRS and the WBPI scores between study baseline and the end of initial titration. To compare incidence of adverse events between study groups, we used the Cochran-Mantel-Haenszel general association test stratified by history of intrathecal opioid use. For adverse events with fewer than 5 reports, we used the Fisher exact test. All statistical tests were 2-sided, and we considered results statistically significant if $P \leq .05$.

The intent-to-treat (ITT) sample included patients who received a study drug and had baseline and follow-up VASPI scores. The evaluable sample had sufficient VASPI data at the end of the initial titration period and did not substantially violate the protocol. Efficacy and demographic results cover the evaluable sample, and safety results cover the ITT sample plus 1 open-label, compassionate-use patient.

RESULTS

The study's first patient was enrolled on March 12, 1996, and the last patient completed the study on July 11, 1998. Patients ages 24 to 85 years were enrolled at 32 study centers. Seven centers enrolled 5 or more patients, 13 centers enrolled 2 to 4 patients, and 12 centers enrolled only 1 patient each. We excluded 3 patients in the ziconotide group because of insufficient VASPI data, leaving an evaluable group of 68 patients receiving ziconotide and 40 receiving placebo, an ITT group of 71 patients receiving ziconotide and 40 receiving placebo, and a total population of 112 patients (including 1 open-label, compassionate-use patient) (FIGURE 1).

More than 25 types of cancer were represented in the patient population, and more than half of the patients had widespread metastatic disease. Many of the nonmetastatic cancers directly infiltrated neural structures, including the spinal cord. The most frequently mentioned cancer complications causing pain were neuropathy, postherpetic neuralgia, pathologic fractures, and complications of cancer radiotherapy. Among the patients with AIDS, the most frequent causes of pain were peripheral neuropathy, Kaposi sarcoma, and postherpetic neuralgia. The majority of patients had undergone 1 or more surgical procedures for cancer excision, including hysterectomy, mastectomy, pneumectomy, and amputation (2 patients had undergone hip disarticulation). Three patients had undergone bone marrow transplantation.

At baseline (TABLE 1) the mean KPSS score was near 60, and 36 patients had received intrathecal morphine. Medication use included a median oral morphine equivalent dosage of 300 mg/d in the ziconotide group and 600 mg/d in the placebo group. Baseline medications included opioids (92% of patients), antidepressants (44%), anxiolytics (40%), anticonvulsants (27%), anti-inflammatory agents (28%), and antipsychotics (16%). The ziconotide and placebo groups had comparable demographic and clinical characteristics, including mean VASPI scores (73.6 [SD, 1.8] mm vs 77.9 [SD, 2.3] mm, respectively; $P = .18$).

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From baseline to the end of the initial titration phase, mean VASPI scores for the evaluable group improved 53.1% (95% confidence interval [CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($P<.001$) (FIGURE 2). Efficacy results in the ITT sample were not appreciably different from those in the evaluable sample; the mean changes in VASPI score for the ITT sample were 51.4% in the ziconotide group and 18.1% (95% CI, 17.3%-49.4%) in the placebo group ($P<.001$).

Pain relief (based on CPRS scores) was moderate to complete in 52.9% of the ziconotide group and in the same range but never reaching complete in 17.5% of the placebo group ($P<.001$). Five patients receiving ziconotide achieved complete pain relief; 50.0% of those receiving ziconotide responded to therapy, compared with 17.5% of those receiving placebo ($P=.001$) (FIGURE 3). Opioid use decreased in the ziconotide group by 9.9% but increased in the placebo group by 5.1%.

From the protocol-defined responder group of 34 patients receiving ziconotide and 7 receiving placebo, 2 patients (1 from each group) did not continue into the maintenance phase. An additional 15 patients receiving ziconotide and 5 receiving placebo were identified as responders by the investigators (though they did not meet strict protocol-defined responder criteria) and proceeded to the maintenance phase. In patients receiving ziconotide who proceeded to the maintenance phase of the study (n=48), ziconotide maintained efficacy, resulting in a 69.2% change in VASPI scores at the end of the initial titration phase, compared with 69.4% at the end of the maintenance phase. The 26 patients receiving placebo who crossed over to the ziconotide group during the second phase experienced a 44.9% mean reduction in VASPI score at the end of the crossover phase. The 12 patients receiving ziconotide who crossed over to the placebo group experienced a 4.2% mean reduction in VASPI score at the end of the crossover phase.

The therapeutic effect (ie, improvement in VASPI score for the ziconotide group minus the improvement for the placebo group) was statistically significant in both starting-dose subgroups and in each underlying disease subgroup (Figure 2). Age, sex, or prior treatment with intrathe-

Table 2. Adverse Events Reported in 5% or More of Patients in the Safety Sample (Initial Titration Phase)

	No. (%)	
Body System/Adverse Event	Ziconotide (n = 72)	Placebo (n = 40)
Patients with any adverse event	70 (97.2)	29 (72.5)
Patients with any serious adverse event	22 (30.6)	4 (10.0)
Body as a whole	33 (45.8)	14 (35.0)
Fever	18 (25.0)	3 (7.5)
Headache	11 (15.3)	6 (15.0)
Asthenia	5 (6.9)	2 (5.0)
Pain	2 (2.8)	2 (5.0)
Injection site reaction	0	2 (5.0)
Cardiovascular system	24 (33.3)	4 (10.0)
Postural hypotension	17 (23.6)	2 (5.0)
Hypotension	6 (8.3)	2 (5.0)
Digestive system	42 (58.3)	16 (40.0)
Nausea	21 (29.2)	7 (17.5)
Vomiting	13 (18.1)	5 (12.5)
Constipation	9 (12.5)	7 (17.5)
Nausea and vomiting	9 (12.5)	0
Anorexia	5 (6.9)	0
Diarrhea	5 (6.9)	2 (5.0)
Dyspepsia	1 (1.4)	2 (5.0)
Metabolic and nutritional system	2 (2.8)	2 (5.0)
Peripheral edema	1 (1.4)	2 (5.0)
Musculoskeletal system	7 (9.7)	1 (2.5)
Myasthenia	6 (8.3)	1 (2.5)
Nervous system	60 (83.3)	14 (35.0)
Dizziness	36 (50.0)	4 (10.0)
Nystagmus	33 (45.8)	4 (10.0)
Somnolence	17 (23.6)	3 (7.5)
Confusion	15 (20.8)	2 (5.0)
Abnormal gait	9 (12.5)	0
Nervousness	7 (9.7)	0
Ataxia	4 (5.6)	1 (2.5)
Insomnia	4 (5.6)	0
Abnormal thinking	4 (5.6)	0
Respiratory system	14 (19.4)	6 (15.0)
Dyspnea	4 (5.6)	2 (5.0)
Lung disorder	4 (5.6)	0
Hypoxia	1 (1.4)	2 (5.0)
Pneumonia	1 (1.4)	2 (5.0)
Skin and appendages	7 (9.7)	4 (10.0)
Pruritus	3 (4.2)	2 (5.0)
Special senses	9 (12.5)	0
Amblyopia	4 (5.6)	0
Urogenital system	23 (31.9)	0
Urinary retention	13 (18.1)	0
Urinary tract infection	7 (9.7)	0

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cal morphine did not affect the improvement in VASPI scores. The treatment groups did not register a significant difference in WBPI subsets or KPSS scores at the end of the initial titration phase.

During the initial titration phase, 4 (10.0%) of the 40 patients receiving placebo reported a total of 4 serious adverse events, and 22 (30.6%) of the 72 receiving ziconotide in the safety group reported a total of 31 serious adverse events. Of these 31 events, we considered the 14 (45.2%) that involved the nervous system (5 moderate, 9 severe) to be related to ziconotide treatment. The remaining serious adverse events were not determined by the reporting investigators to be related to ziconotide treatment. The most common serious adverse events for patients who received ziconotide during the initial titration phase were confusion, somnolence, and urinary retention (4.2% each); all others were reported in less than 3% of the study population.

Nine types of adverse events occurred with significantly greater frequency in the ziconotide group compared with the placebo group (TABLE 2), but starting at the lower dosage, using smaller dose increments, and increasing the interval between dose titrations tended to reduce this frequency. TABLE 3 shows the proportion of patients in each starting dosage group that experienced these adverse events. Confusion was the only of these 9 adverse events that occurred in a larger percentage of patients with a starting ziconotide dosage of 0.1 µg/h or less compared with patients with a starting ziconotide dosage of more than 0.1 µg/h.

Table 3. Ziconotide-Specific Adverse Events in the Safety Sample, by Starting Dosage

	Adverse Events, No. (%)			
	Ziconotide		Placebo	
Event	>0.1 µg/h (n = 31)	≤0.1 µg/h (n = 41)	>0.1 µg/h (n = 19)	≤0.1 µg/h (n = 21)
Fever	10 (32.3)	8 (19.5)	1 (5.3)	2 (9.5)
Postural hypotension	10 (32.3)	7 (17.1)	1 (5.3)	1 (4.8)
Nausea	13 (41.9)	8 (19.5)	5 (26.3)	2 (9.5)
Nausea and vomiting	5 (16.1)	4 (9.8)	0	0
Vomiting	9 (29.0)	4 (9.8)	2 (10.5)	3 (14.3)
Abnormal gait	5 (16.1)	4 (9.8)	0	0
Confusion	6 (19.4)	9 (22.0)	1 (5.3)	1 (4.8)
Dizziness	18 (58.1)	18 (43.9)	2 (10.5)	2 (9.5)
Somnolence	9 (29.0)	8 (19.5)	1 (5.3)	2 (9.5)
Urinary retention	7 (22.6)	6 (14.6)	0	0

Table 4. Dose and Timing of Onset of Most Frequent Ziconotide Adverse Events

Adverse Event	No.	Mean (SE) No. of Days to Onset	Mean (SE) Dosage at Onset, µg/h	Mean (SE) Cumulative Dose at Onset, µg
Urinary retention	13	2.23 (0.5)	1.44 (0.8)	37.4 (17.3)
Amblyopia	6	2.33 (0.5)	1.41 (1.0)	42.4 (21.0)
Nausea	34	2.44 (0.3)	0.89 (0.2)	34.2 (11.0)
Somnolence	17	2.47 (0.3)	0.84 (0.2)	30.8 (9.3)
Dizziness	36	2.50 (0.2)	0.97 (0.2)	27.3 (5.0)
Hypotension	23	2.70 (0.4)	1.38 (0.6)	54.3 (19.0)
Nystagmus	33	2.76 (0.2)	1.45 (0.6)	51.3 (19.8)
Confusion	15	3.00 (0.4)	0.62 (0.1)	39.8 (14.0)
Asthenia	11	3.18 (0.5)	1.01 (0.4)	44.9 (12.5)
Abnormal gait	13	3.31 (0.4)	1.14 (0.2)	45.0 (11.6)

TABLE 4 shows the mean dose and timing of onset for the most frequently reported adverse events in patients receiving ziconotide. Confusion occurred much more often in patients receiving ziconotide who were older than 60 years than in those aged 60 years or younger. Central nervous system adverse events (ie, cognitive dysfunction, vestibular symptoms, and somnolence) had a median time to resolution of 4 days (range, 0-58 days). Adverse events led to early discontinuation in 12 patients receiving ziconotide and in 4 receiving placebo. An additional 15 patients receiving ziconotide and 5 receiving placebo discontinued the study for such reasons as external catheter complications, patient request, unrelated medical conditions, or lack of therapeutic effect. There were 5 cases of meningitis in the ziconotide group and 2 in the placebo group—all in patients with external infusion systems.

Thirteen patients died during the study or the 30-day follow-up period, and we recorded 2 additional deaths after follow-up (TABLE 5). Death rates were not significantly different between the ziconotide and placebo groups. Twelve patients died from cancer, 1 committed suicide, 1 succumbed to pneumonia, and 1 died from an unknown cause. Of the 5 patients who died while receiving placebo, 2 had crossed over from the ziconotide group. The patient who died due to unknown causes received only placebo.

Other than these deaths, no clinically significant changes in vital signs, laboratory analyses, or cognitive function test scores occurred in either treatment group from baseline to study termination. There were no reports of anaphylaxis or hypersensitivity to ziconotide.

COMMENT

We demonstrated the clinically and statistically significant analgesic effect of intrathecal ziconotide in a heterogeneous, complex, and treatment-refractory patient population. Our results validate reports of the antinociceptive effects of ziconotide,[12,13]

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Table 5. Deaths Reported During the Study and Within 30 Days Poststudy

Patient Sex, Age	No. of Days Receiving Ziconotide	No. of Days Receiving Placebo	No. of Days After Last Dose Until Death	Cumulative Ziconotide Dose, µg	Cause of Death	Relationship to Treatment
Initial Titration Phase						
Ziconotide						
Female, 59 y	4	. . .	55	80.40	Carcinoma of lung	Unrelated
Male, 51 y	3	. . .	1	116.40	Carcinoma of lung	Underlying condition
Placebo						
Female, 53 y	. . .	5	40	Unknown	Unknown	Unknown
Maintenance Phase						
Ziconotide						
Female, 66 y	11	. . .	15	166.57	Endometrial carcinoma	Unrelated
Female, 57 y	9	. . .	0	26.09	Carcinoma	Unrelated
Female, 53 y	10	. . .	2	84.40	Carcinoma of lung	Unrelated
Female, 45 y	10	. . .	4	40.06	Endometrial carcinoma	Unrelated
Male, 63 y	8	. . .	3	531.26	Suicide	Possible
Placebo						
Male, 40 y	. . .	11	13	0	Carcinoma	Unrelated
Crossover Phase						
Ziconotide						
Male, 60 y	5	5	29	36.07	Prostatic carcinoma	Unrelated
Male, 55 y	5	5	20	20.70	Carcinoma of lung	Unrelated
Male, 67 y	5	1	7	33.21	Pneumonia	Probable
Placebo						
Female, 52 y	5	5	7	78.60	Breast carcinoma	Underlying condition
Male, 70 y	5	5	3	24.13	Carcinoma of lung	Underlying condition
Male, 70 y	5	6	8	58.39	Carcinoma of lung	Unrelated

as well as the findings of an open-label feasibility study in patients with intractable pain.[2] Animal studies suggested that our patients would not develop tolerance to the analgesic effects of ziconotide within the time frame of this trial, perhaps because ziconotide binds directly to calcium channels, bypassing G-protein–dependent secondary messenger mechanisms.[13]

The robust analgesic effect of ziconotide observed in our study population underscores the finding that intrathecal ziconotide is 1000-fold more potent than intrathecal morphine in blocking the phase-2 responses in the formalin test that are thought to depend on central sensitization.[12]

Because this was a safety and efficacy study, we deliberately maximized the incidence of ziconotide adverse events. Ziconotide produced significantly more vestibular effects (eg, somnolence, confusion, urinary incontinence, and fever) than did placebo, perhaps because ziconotide blocks N-channels in the granular cell layer of the cerebellum.[16] These effects were easily recognizable and reversible, however, and their incidence decreased when we decreased the initial dose and the frequency of titration.

The incidence of meningitis in this trial can be attributed to 2 factors. First, the study patients were very likely immunosuppressed. Second, the limited life expectancy of many of the patients made it prudent to administer ziconotide via implanted catheter or external infusion systems or via preexisting implanted pumps. Each of the 7 cases of meningitis occurred in patients with external systems. Thus, the high rate of infection appears to be due to poor physiological status and presence of an externalized catheter, not to an idiosyncratic effect of the drug.

The overall frequency of deaths in our study was consistent with the underlying disease status of the patients.

Our randomized, double-blind, placebo-controlled trial revealed the considerable efficacy of ziconotide in patients with end-stage cancer or AIDS and with refractory pain. Compared with placebo, ziconotide was associated with a number of (typically dose-related) adverse events: abnormal gait, dizziness, nystagmus, confusion, somnolence, fever, postural hypotension, urinary retention, nausea, and vomiting. Completed and ongoing trials using lower dosages of ziconotide and longer durations of treatment will better define the long-term risk-benefit profile of this potent analgesic.

Author Contributions: Dr Staats, as principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Staats, Wallace, Mangieri, Luther, McGuire.
Acquisition of data: Staats, Yearwood, Charapata, Presley, Wallace, Byas-Smith, Fisher, Bryce, Mangieri, Luther, Mayo, McGuire, Ellis.
Analysis and interpretation of data: Staats, Mangieri, Luther, Mayo, McGuire, Ellis.
Drafting of the manuscript: Staats, Mangieri, Mayo, Ellis.
Critical revision of the manuscript for important intellectual content: Staats, Yearwood, Charapata, Presley, Wallace, Byas-Smith, Fisher, Bryce, Luther, McGuire, Ellis.
Statistical expertise: Ellis.
Obtained funding: Luther, Mayo, McGuire.
Administrative, technical, or material support: Staats, Luther, Mayo, Ellis.

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Study supervision: Staats, Presley, Fisher, Mangieri, Luther, Mayo, McGuire.

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Role of the Sponsor: The study sponsor at the time of the initiation of the trial was Neurex. The sponsor designed the study with the advice of physician investigators who were expert in the use of intrathecal therapy. The sponsor was responsible for the overall conduct of the study and the collection, analysis, and interpretation of the data obtained. Contract research organizations (IBAH Inc and Clinmetrics) were responsible for the monitoring of the trial and the study sites, the resolution of data queries, and the transfer of completed case report forms to the data management group. Data management was performed by Covance and included data entry, statistical analysis, and generation of data tables and listings. The preparation of the final trial report was performed jointly by Covance and the sponsor. The preparation and review of the manuscript were a joint effort among the authors, the sponsor, and a contract medical writer. Elan pharmaceuticals provided financial support for the medical writer. All pertinent original data tables and listings from the trial were provided to the corresponding author for his use in the preparation and review of the manuscript. Medtronic was responsible for providing SynchroMed infusion systems and for analyzing and reporting the performance of the SynchroMed infusion system.

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