

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY OF INTRATHECAL ZICONOTIDE FOR THE TREATMENT OF SEVERE CHRONIC PAIN IN ADULTS

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ABSTRACT

Introduction

Ziconotide is a nonopioid, N-type calcium channel blocker. Research suggests that ziconotide inhibits neuronal calcium influx, thereby reducing neurotransmitter release at primary pain afferents. A randomized, double-blind, placebo-controlled, multicenter trial was conducted to assess the analgesic efficacy and safety of intrathecal (IT) ziconotide utilizing a slow-titration, low-dose schedule in patients with refractory, severe, chronic pain.

Materials and Methods

After weaning of all IT medications and stabilization on IT saline for 1 week, patients with a Visual Analog Scale of Pain Intensity (VASPI) score ≥ 50 mm were randomized to ziconotide or placebo. Ziconotide was initiated at a dosage of 2.4 mcg/d (0.1 mcg/h) and titrated to analgesia in increments ranging from 0.05 to 0.1 mcg/h. Upward titration could occur at intervals no less than 24 hours, 2 to 3 times per week, until analgesia or the maximum allowed dosage (21.6 mcg/d, 0.9 mcg/h) was attained. Primary efficacy was measured by mean percent change of VASPI score from baseline to the end of titration (Week 3). Satisfaction with treatment and pain relief were assessed with Clinical Global Impression (CGI) scales. Adverse events (AEs) were recorded throughout the study to monitor safety.

Results

A total of 112 ziconotide and 108 placebo patients were randomized; 92% of patients completed treatment. At study termination, mean dosage was 6.96 mcg/d (0.29 mcg/h) in the ziconotide group and 8.94 mcg/d (0.41 mcg/h) in the placebo group. Mean VASPI score was 80.7 mm at baseline for both groups. After 3 weeks, the mean percent improvement in VASPI score was 14.7% for ziconotide patients and 7.2% for placebo patients ($p=0.036$, two-sample t test). On the CGI scales, a significantly higher percentage of ziconotide (28.4%) than placebo patients (12.1%) reported "a lot" or "complete" satisfaction with treatment ($p=0.0027$, Mantel-Haenszel chi-square test) and "very good" or "excellent" pain control (11.9% and 0.9%, respectively; $p=0.0004$, Mantel-Haenszel chi-square test). The discontinuation rate due to AEs was 5.4% ($n=6$) in ziconotide-treated patients and 4.6% ($n=5$) in the placebo-treated patients. The majority (84%) of AEs were mild to moderate in severity; the most frequently reported ziconotide-related AEs were dizziness (34.8%), nausea (19.6%), and confusion (14.3%). During the treatment period, 11.6% ($n=13$) of patients in the ziconotide group reported a total of 19 serious AEs (SAEs) and 9.3% ($n=10$) of patients in the placebo group reported a total of 25 SAEs.

Conclusions

Treatment-refractory patients showed significantly improved pain levels, patient satisfaction, and overall pain control with treatment with IT ziconotide versus placebo. Ziconotide-treated patients reported primarily mild to moderate AEs. Discontinuation rates due to AEs were similar between the ziconotide- and placebo-treated patients.

INTRODUCTION

Many patients with severe chronic pain fail to receive satisfactory pain relief with systemic or intrathecal (IT) opioid therapy.^{1,2} Ziconotide (PRIALT[®]; ziconotide intrathecal infusion), the synthetic equivalent of a 25-amino-acid polybasic peptide originally found in the venom of *Conus magus*, a marine snail,³ is a nonopioid analgesic. Ziconotide was recently approved by the United States Food and Drug Administration for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine.⁴ Two initial double-blind, placebo-controlled trials were conducted utilizing a high-dose, fast-titration regimen.^{5,6} The fast titration led to statistically

significantly more Serious Adverse Events (SAEs) and a higher discontinuation rate for the ziconotide-treated patients than placebo-treated patients. The current study was designed to evaluate the safety and efficacy of ziconotide utilizing a slower titration schedule and lower maximum dosage than was used in the 2 previous controlled trials.

METHODS

This double-blind, placebo-controlled, randomized study included patients meeting the criteria in Table 1. The trial design is shown in Figure 1. Patients were randomized in a 1:1 ratio to receive ziconotide or placebo. The planned and actual ziconotide dosing schedule is shown in Figure 2. The actual mean dose was approximately 1/3 of the maximal allowed dose for the study.

The primary efficacy variable was the mean percent change in the Visual Analog Scale of Pain Intensity (VASPI) score from baseline (ie, the end of the stabilization period) to the end of Week 3. Secondary efficacy measurements included the mean percent change in VASPI score from baseline to the end of Weeks 1 and 2, scores on the Clinical Global Impression (CGI) Satisfaction and Overall Pain Control items at study termination, and the percentage of treatment responders (ie, patients with a $\geq 30\%$ improvement in VASPI score from baseline to the end of Week 3). Weekly opiate use was recorded and was converted to oral morphine equivalents using established conversion factors. Safety was evaluated by reports of AEs, clinical laboratory evaluations, vital signs, and 12-lead electrocardiograms (ECGs).

The intent-to-treat population, which included all randomized patients, was used for the safety and efficacy analyses. For the mean percent change in VASPI score from baseline to the end of Weeks 1, 2, and 3, the last observation carried forward (LOCF) method was used, in which a patient's last observed score was used in place of a missing score. Missing data were not imputed for other outcome measurements.

The mean percent change from baseline on the VASPI was compared between groups using a two-sample t test. The distribution of CGI responses in the 2 treatment groups was compared using the Mantel-Haenszel chi-square test with 1 degree of freedom. Pearson's chi-square test was used to compare the proportion of treatment responders in the 2 groups. The percent change in weekly opiate consumption from the pretreatment stabilization period was evaluated using a two-sample t test. Fisher's exact test was used to evaluate AEs reported by 10% or more patients in each group. All statistical tests were two-sided, and results were considered significant if $p \leq 0.05$.

Table 1. Main Inclusion/Exclusion Criteria

Main Inclusion Criteria

- VASPI score ≥ 50 mm
- Severe chronic pain not adequately controlled and/or patient was intolerant to systemic opioids
- Pain that warranted the use of IT therapy
- Patient had an implanted programmable SynchroMed[®] Infusion System in place for the treatment of chronic pain
- At randomization, the patient had been weaned off of all IT medications and stabilized on systemic analgesics for at least one week

Main Exclusion Criteria

- Patient was pregnant or lactating
- Patient had a known hypersensitivity to ziconotide or any of the excipients in the formulation

VASPI=Visual Analog Scale of Pain Intensity.

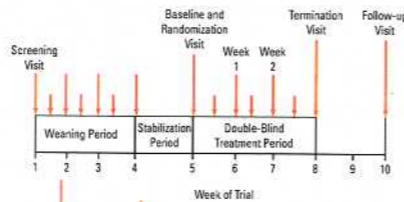


Figure 1. Trial design.

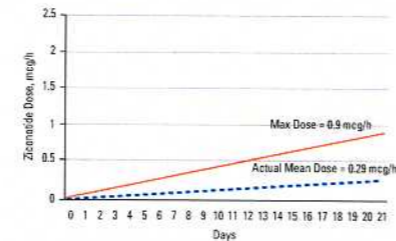
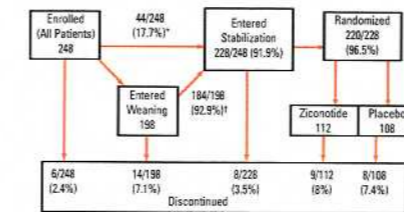


Figure 2. Planned and actual ziconotide dosing schedule. Ziconotide was titrated in 0.05- to 0.1-mcg/h increments, with at least 24 hours between each dosage increase.

RESULTS

Of the 248 patients enrolled in the study, 220 were randomized to receive ziconotide or placebo (Figure 3). Dosing of study drug is shown in Figure 4. Mean percent improvement from baseline in VASPI score was significantly greater for the ziconotide group than the placebo group at the end of Weeks 1 and 3 (Figure 5). Responder rates did not differ between groups. The ziconotide group showed significantly better satisfaction and pain control compared with the placebo group based on CGI scores (Figure 6). Mean weekly opiate use (expressed in oral morphine equivalents) decreased in both groups (Figure 7). There was a 23.7% mean decrease in weekly opiate use from the pretreatment stabilization period at Week 3 for the ziconotide group compared to a 17.3% decrease in the placebo group ($p=0.4371$, two-sample t test). The most commonly reported AEs are listed in Table 2. The most frequently reported ziconotide-related AEs were dizziness (34.8%), nausea (19.6%), and confusion (14.3%). Most AEs (83.6% ziconotide, 83.9% placebo) were mild or moderate in severity. The discontinuation rate due to AEs during treatment was comparable between the ziconotide ($n=6$, 5.4%) and placebo groups ($n=5$, 4.6%; $p=0.8045$, Pearson's chi-square test). During the treatment period similar numbers of placebo- and ziconotide-treated patients reported serious adverse events ($n=10$, 9.3% and $n=13$, 11.6%, respectively). No significant changes in vital signs or ECGs were noted. Laboratory evaluations were generally unremarkable. Thirty-seven percent of

ziconotide-treated patients and 10% of placebo-treated patients had elevated creatine kinase (CK). Creatine kinase elevations greater than three times the upper limit of normal were observed in 4.5% of the ziconotide-treated patients and none in the placebo-treated patients ($p=0.0597$, Fisher's exact test).



* 44 patients did not require IT medication weaning and entered the stabilization period directly.

† 194 patients completed the weaning period and entered the stabilization period.

Figure 3. Patient disposition and study termination by treatment group.

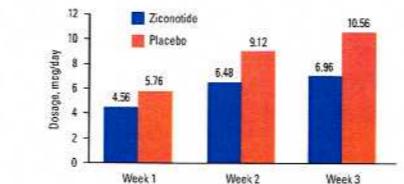
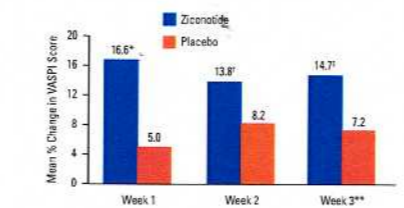


Figure 4. Mean dosage (mcg/day) of study drug by week.

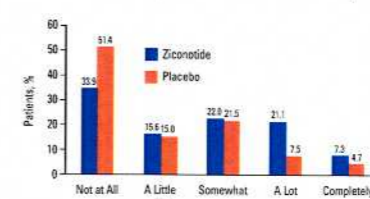


Ziconotide and placebo groups were compared using two-sided two-sample t tests: * $p=0.0026$, $p=0.1211$, and $p=0.0386$.

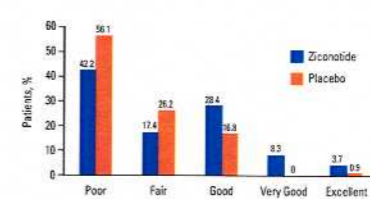
**primary efficacy outcome measure

Figure 5. Mean percent improvement in VASPI score from baseline to Weeks 1, 2, and 3.

A Clinical Global Impression: Satisfaction with Therapy

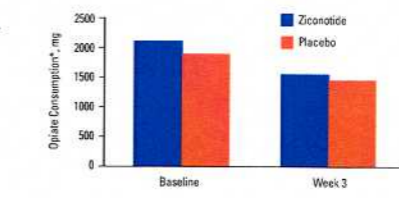


B Clinical Global Impression: Overall Pain Control



For Satisfaction With Therapy (A) and Overall Pain Control (B), the difference between the 2 treatment groups was statistically significant ($p=0.0027$ and $p=0.0004$, respectively; comparisons were made using Mantel-Haenszel mean score tests assuming equally spaced categories).

Figure 6. Percentage of patients reporting on the CGI at study termination.



*Opiate consumption in oral morphine equivalents.

Figure 7. Mean weekly opiate consumption.

Table 2. Most Frequently Reported AEs During the Treatment Period (Incidence $\geq 10\%$ in Any One Treatment Group)

Adverse Event	Ziconotide (n=112)	Placebo (n=108)
Any AE	104 (92.9)*	89 (82.4)
Any serious AE	13 (11.6)	10 (9.3)
Dizziness	53 (47.3)*	14 (13.0)
Nausea	46 (41.1)	33 (30.6)
Asthenia	25 (22.3)	13 (12.0)
Somnolence	25 (22.3)	16 (14.8)
Diarrhea	21 (18.8)	18 (16.7)
Confusion	20 (17.9)*	5 (4.6)
Ataxia	18 (16.1)*	2 (1.9)
Headache	17 (15.2)	13 (12.0)
Vomiting	17 (15.2)	14 (13.0)
Abnormal gait	17 (15.2)*	2 (1.9)
Memory impairment	13 (11.6)*	1 (0.9)
Pain	12 (10.7)	8 (7.4)
Creatine kinase increased	12 (10.7)	4 (3.7)
Pruritis	9 (8.0)	11 (10.2)
Insomnia	7 (6.3)	13 (12.0)

*Occurred with significantly greater frequency with ziconotide versus placebo administration, $p \leq 0.05$ (Fisher's exact test).

CONCLUSIONS

In this study, patients with refractory severe chronic pain who were treated with IT ziconotide achieved significant reductions in the VASPI compared with those patients treated with IT placebo. Although the degree of pain relief, as measured by the VASPI, noted in this study was lower than that noted in the 2 previous controlled clinical trials of ziconotide,^{5,6} the slower titration regimen and lower dosages used in the current study probably explain this lower mean between-group difference. However, this low-dose, slow titration study resulted in better patient retention and an improved safety profile. These findings suggest that the best treatment outcome may be achieved with slow titration of ziconotide at low dosages in order to identify each patient's individualized therapeutic window. Intrathecal ziconotide is the first new treatment for patients with severe chronic pain in 20 years supported by double-blind, placebo-controlled clinical studies.

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