

Single-shot Bolus Trialing to Assess Patient Response to Intrathecal Ziconotide

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Abstract

Introductions: Intrathecal (IT) infusion of ziconotide is approved for treating severe chronic pain refractory to other treatment modalities. Previous clinical experience gained with IT ziconotide resulted in serious adverse events (AEs) leading to treatment discontinuation. We designed a study to evaluate single-shot injection as a trialing method to assess the effectiveness and tolerability of ziconotide prior to continuous infusion via the patient's implanted medication infusion pump and to examine the relationship between the effective single-shot dose and the effective long-term infusion dose.

Methods: Adult patients with chronic non-malignant pain receiving high-dose IT opioids and/or who were dissatisfied with IT/systemic opioid treatment were candidates for this open-label study. The 2 phases of the study included single-shot escalating-dose trialing and continuous infusion. After the single-shot trial (1 mcg, 3 mcg, or 5 mcg), participants logged their pain scores at 0, 1, and 24 hours and completed a patient satisfaction questionnaire. At 24 hours post-trial, subjects could discontinue, schedule for the next higher single-shot dose, or opt to add IT ziconotide to their IT infusion regimen if they experienced at least 50% improvement and were satisfied. Once ziconotide infusion was initiated, efficacy and AEs were monitored periodically for 6 months, with ziconotide dose adjustments made as needed.

Results: Of 42 patients who enrolled, 26 were female and mean age was 57.1 years. The mean baseline pain score on the numeric rating scale (NRS) was 6.5 (SD 2.3), and the mean Oswestry Questionnaire score was 55.3 (SD 13.3). Thirty patients received the first ziconotide single-shot trial (1 mcg), after which the mean NRS score was reduced by 28.5% at 1 hour and 16.7% at 24 hours. Six patients discontinued, 14 added IT ziconotide infusion to their treatment regimens (1-mcg trial group), and 10 received the next single-shot dose. For the 10 patients who received the 3-mcg dose, mean pain NRS score was reduced by 20.3% at both 1 and 24 hours. Three of these patients discontinued, 4 added IT ziconotide to their IT treatment regimens (3-mcg trial group), and 3 received the final single-shot trial dose. One patient who received the 5-mcg bolus dose chose to add IT ziconotide (5-mcg trial group). Bolus doses of ziconotide were well tolerated in general. The most common AE cited for study discontinuation after single-shot injection was nausea/vomiting.

At 6 months, 13 patients were still receiving IT ziconotide infusion and mean NRS score was reduced by 13.8%. All 3 trial groups showed an increase in daily maintenance dose at each data collection point (mean 2.0–2.9 mcg/day). The daily dose did not reach the trial bolus dose for the 3-mcg or 5-mcg trial study groups.

Discussion: Our data demonstrate that single-shot ziconotide trials of 1 mcg and 3 mcg are safe and effective in determining patient response to the drug, while there is no additional benefit of the 5-mcg trial dose. As with IT morphine and baclofen, single-shot bolus trialing provides physicians and patients an opportunity to experience the effects of IT ziconotide before committing to a continuous IT infusion in this heterogeneous, complex, and treatment-refractory population, although there is no clear relationship between the successful trial dose and the long-term infusion dose.

Introduction

- Prialt® (ziconotide **intrathecal infusion**, Azur Pharmaceuticals, Philadelphia, PA), which inhibits N-type calcium channels and is believed to reduce signaling along the spinal pain pathways when administered by intrathecal (IT) infusion.^{1,4}
- In patients with severe chronic pain refractory to IT morphine or other treatment modalities, a preliminary ziconotide trial may be performed before initiating continuous infusion via the patient's implanted medication infusion pump to assess patient response.⁵⁻⁷

Methods

- We designed a study to:
 - Evaluate patients' response to a graduated, single-shot bolus trialing method for effectiveness and tolerability of ziconotide prior to continuous infusion via an IT infusion pump.
 - Examine the relationship between the effective single-shot dose and the effective long-term infusion dose.
- All subjects received the single-shot IT injection in the ambulatory setting, administered under fluoroscopy guidance by the primary investigator using a 20-gauge short bevel Tuohy needle.
 - The needle was introduced at the L1-2 interspace, the subarachnoid space accessed, cerebral spinal fluid aspirated, and the needle rotated 90 degrees so the bevel was positioned in a cephalad orientation.
 - A myelogram was performed on all subjects to confirm needle placement prior to injection of the drug diluted in 2 cc of preservative-free saline.
- Following the procedure, all subjects were monitored for side effects for 60 minutes.

- At 24 hours after each single-shot trial in this open-label study, subjects could discontinue, schedule for the next higher single-shot dose, or if they experienced at least 50% pain improvement and were satisfied, opt to add ziconotide to their continuous IT infusion treatment regimens.
- Once ziconotide continuous infusion was initiated, efficacy and adverse events (AEs) were monitored periodically for 6 months, and ziconotide dose adjustments were made based on patient response and analgesia.

Results

- Patient demographics and baseline characteristics are presented in **Table 1**.

Table 1. Patient Demographics and Baseline Characteristics

Number of patients screened, N	42		
Sex, N (%)	Male	16	38.1%
	Female	26	61.9%
Age, mean (range)	57.1	(40–77)	
Pain classification, N (%)	FBSS	19	45.2%
	DDD	13	30.9%
	LBP	7	16.6%
	Other	3	7.1%
NRS pain score	Mean (SD)	6.5	(2.3)
	Median (range)	6	(1–10)
Oswestry questionnaire	Mean (SD)	55.3	13.3
	Median (range)	56.9	(24.4–76.0)

DDD = degenerative disk disease, FBSS = post-laminectomy syndrome, LBP = low back pain, NRS = numerical rating scale

Trialing phase

- 30/42 patients completed the first single-shot trial (1 mcg) (**Table 1, Figure 1**).
 - Mean pain NRS score was reduced by 20% at 1 hour and by 16% at 24 hours (**Figure 2**).
 - 14 patients added ziconotide IT infusion to their treatment regimens (1-mcg trial group) (**Figure 3**).^{*}
 - 6 patients discontinued the study.
- 10 patients received the next single-shot trial (3 mcg).
 - Mean pain NRS score was reduced by 10% at 1 hour and by 18% at 24 hours (**Figure 2**).
 - 4 patients added ziconotide IT infusion to their treatment regimens (3-mcg trial group) (**Figure 3**).
 - 3 patients in the 3-mcg group discontinued the study.
- 3 patients received the final single-shot trial (5 mcg).
 - 2 patients experienced no change in mean pain score at 1 hour or 24 hours (NRS=9 and 10, respectively), and 1 patient experienced a 2-point decrease (NRS=7 at 0 hr, NRS=5 at both 1 hr and 24 hr).
 - One patient chose to add ziconotide to their IT infusion treatment regimen (**Figure 2**).

- Single-shot doses of ziconotide were well tolerated in general.
- Patients experienced known side effects of ziconotide such as nausea, vomiting, dizziness, and somnolence. Some patients were unwilling to proceed to continuous infusion after the trial due to these known side effects.
- In the 1-mcg and 3-mcg single-shot trials, the reason for discontinuation from further trialing in all instances was one or more AEs.
 - The AEs most commonly cited as reasons for discontinuation were nausea/vomiting and dizziness.

Continuous infusion phase

- At 6 months, 13 (72%) patients who completed the trialing study were still receiving ziconotide IT infusion, while 5 had discontinued ziconotide.
- Mean pain NRS score had been reduced from 6.5 at baseline to 5.6 at 6 months from baseline (13.8% reduction) (**Table 2**).

^{*}One patient from this group was awaiting approval for pump implantation when the study closed and therefore is not included in the Study Map (**Figure 1**).

- All 3 of the trial study groups showed increases in the mean daily maintenance dose of ziconotide at each data collection point (**Figure 4**).
 - Mean daily maintenance dose for the 1-mcg trial study group exceeded the trial dose after 2 months, while mean daily maintenance dose for the 3-mcg or 5-mcg ziconotide trial study groups never reached the trial bolus dose.
 - Patients who discontinued continuous ziconotide infusion frequently did so due to known adverse effects of ziconotide such as abnormal vision, confusion, dizziness, memory impairment, nausea, somnolence, vomiting, and weakness.

Figure 1. Study map.

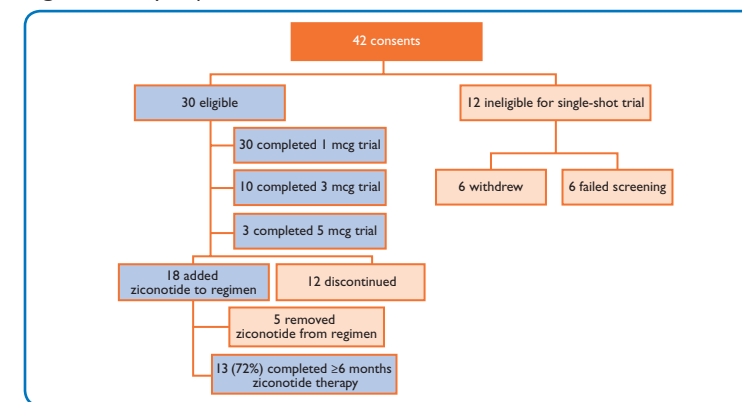


Figure 2. Mean pain NRS scores for each single-shot trial at times 0 hour, 1 hour, and 24 hours.

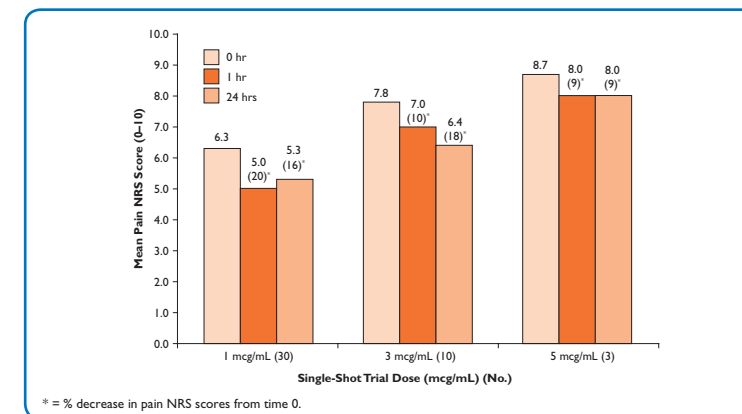


Figure 3. Patients' treatment choices by trialing group.

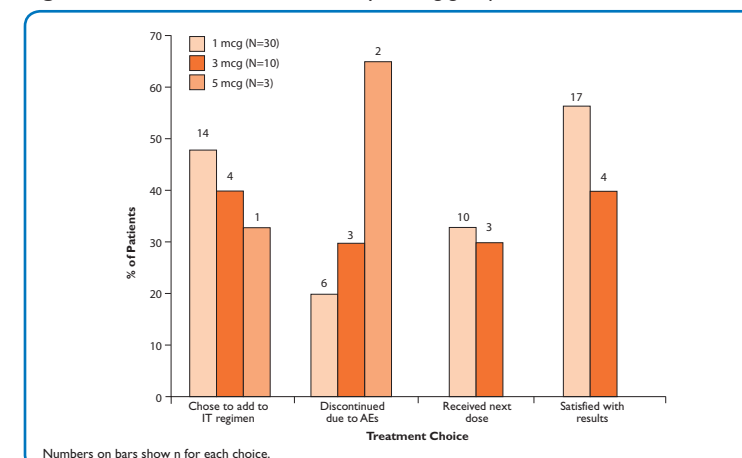
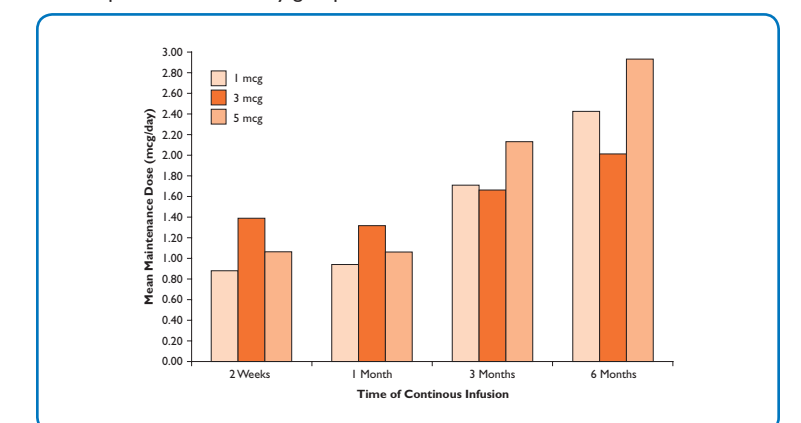


Table 2. Mean Pain NRS Scores, Oswestry Questionnaire Scores, and Daily Dose of IT Ziconotide From Baseline to End of Study

	Baseline	2 Weeks	1 Month	3 Months	6 Months
Study population, N	42	17	16	14	13
Pain NRS score, 0–10 mean (SD)	6.5 (2.3)	5.9 (2.3)	5.0 (2.5)	5.7 (2.1)	5.6 (2.5)
Oswestry questionnaire score, % mean (SD)	53.3 (16.4)	N/A	N/A	56.9 (11.2)	N/A
Ziconotide dose, mcg/day mean (SD)	N/A	0.74 (0.12)	2.06 (0.09)	1.85 (0.63)	2.35 (0.98)

Figure 4. Mean daily maintenance doses (mcg/d) of ziconotide during continuous infusion phase in 3 trial study groups.



Discussion

- The results demonstrate that single-shot ziconotide trials of 1 mcg and 3 mcg are safe and effective for determining patient response to the drug, while there is no additional benefit of the 5-mcg trial dose.
- There is no clear relationship between the successful trial dose and the long-term infusion dose.
- It may be useful to consolidate information on various methods for trialing ziconotide to provide guidance to physicians who would like to offer ziconotide trialing to their patients.

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