Received: January 19, 2012 Revised: June 30, 2012 Accepted: October 4, 2012

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12003

Bolus Intrathecal Injection of Ziconotide (Prialt®) to Evaluate the Option of Continuous Administration via an Implanted Intrathecal Drug Delivery (ITDD) System: A Pilot Study

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Objectives: This study evaluated efficacy and safety of bolus doses of ziconotide (Prialt®, Eisai Limited, Hertfordshire, UK) to assess the option of continuous administration of this drug via an implanted intrathecal drug delivery system.

Materials and Methods: Twenty adults with severe chronic pain who were under consideration for intrathecal (IT) therapy were enrolled in this open label, nonrandomized, pilot study. Informed consent was obtained. Demographics, medical/pain history, pain scores, and concomitant medications were recorded. A physical examination was performed. Creatine kinase was measured. Initial visual analog scale (VAS), blood pressure, heart rate, and respiratory rate were recorded. All patients received an initial bolus dose of 2.5 mcg ziconotide; the dose in the subsequent visits was modified according to response. Subsequent doses were 2.5 mcg, 1.2 mcg, or 3.75 mcg as per protocol. A good response ($\geq$30% reduction in baseline pain VAS) with no side-effects on two occasions was considered a successful trial. Data were analyzed using a generalized estimating equations model, with pain VAS as the outcome and time (seven time points; preinjection and one to six hours postinjection) as the predictor.

Results: Generalized estimating equations analysis of summary measures showed a mean reduction of pain VAS of approximately 25% at the group level; of 11 responders, seven underwent pump implantation procedure, two withdrew because of adverse effects, one refused an implant, and one could not have an implant (lack of funding from the Primary Care Trust).

Conclusions: Our data demonstrated that mean VAS was reduced by approximately 25% at the group level after IT ziconotide bolus. Treatment efficacy did not vary with sex, center, age, or pain etiology. Ziconotide bolus was generally well tolerated. Larger studies are needed to determine if bolus dosing with ziconotide is a good predictor of response to continuous IT ziconotide via an intrathecal drug delivery system.

Keywords: Creatine kinase (CK), intrathecal drug delivery (ITDD) system, visual analog score (VAS), ziconotide

Conflict of Interest: S. Eldabe and K.H. Simpson both have received honoraria for presentations and lecture from Eisai UK/Europe. S. Eldabe has done some consulting work for Eisai. Eisai are part funding M. Brookes' MSc. H. Radford received honorarium for presentations and lectures on Ziconotide from Eisai Europe. Neither E. Buchser nor C. Perruchoud has any conflict of interest related to this article.

BACKGROUND

Ziconotide is the only N-type voltage-sensitive calcium channel blocker approved for use in severe refractory chronic pain (1,2). It is a neuroactive peptide, the synthetic equivalent of the conopeptide MVIIa, of the venom fish hunting marine snail, *Conus magus*. It is a highly potent, nonopioid, nonaddictive analgesic with a very narrow therapeutic window (3). The analgesic efficacy and safety have been established in three randomized, double blind, placebo-controlled trials in severe pain due to AIDS, cancer, and non-malignant conditions (4–6). The 2007 polyanalgesic consensus rec-

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ommended ziconotide as one of three options for first-line intrathecal (IT) monotherapy (7). The approved indication by the US Food and Drug Administration is for patients with severe chronic pain in whom IT is considered and who are intolerant of conventional analgesia, adjuvant therapies, and IT morphine (8).

Based on the polyanalgesic initiative and British Pain Society guidelines on IT therapy (9,10), an IT trial is generally recommended before an implant. It provides an opportunity to assess the benefits and side-effects of IT therapy before the patient progresses to long-term infusion. Trials can be performed by single bolus injections or by continuous IT infusions with external catheters. There is no consensus regarding the merit of bolus doses compared with continuous infusions for trials. This decision is based on clinical judgment, local facilities, and practice environments, and is sometimes influenced by insurance issues (11). Infusion trials are more expensive, associated with increased risk of meningitis, and are inconvenient for the patient and physician. There are a few trials of ziconotide by IT bolus (12–14). We report our experience with ziconotide boluses before IT implant.

MATERIALS AND METHODS

Twenty adults with severe chronic pain who were under consideration for IT therapy were assessed for inclusion in this open label, nonrandomized, pilot study in two sites in the UK (James Cook University Hospital Middlesbrough and Leeds Teaching Hospitals). A patient information sheet was provided one to seven days before their planned visit. Ethical approval was obtained from Regional Ethics Committees. Inclusion criteria were male or female patients, aged 18–75 years, with intractable chronic pain, who had failed conventional medical management, were under consideration for intrathecal drug delivery (ITDD), and had the capacity to make informed decisions regarding ITDD with ziconotide. Exclusion criteria were inability to make an informed decision, contraindications to ITDD, allergy to ziconotide, history of psychological disorders, pregnancy, and women with childbearing potential who were not using an effective form of birth control.

Each patient received an IT bolus below L1-L2 level with x-ray guidance if required. IT placement was confirmed by free flow of cerebrospinal fluid. Intravenous access was established until the time of discharge. Patients were admitted to a day case facility on two or three separate occasions, a week apart, for boluses of ziconotide. All patients received a starting bolus dose of ziconotide 2.5 mcg; the dose in subsequent weekly visits was modified based on response. Sequential bolus doses were 2.5 mcg, 1.2 mcg, or 3.75 mcg administered over a three-week period as per protocol (Fig. 1).

If two injections of 2.5 mcg produced a similar analgesic effect with no significant side-effects, long-term ziconotide was considered a realistic option. If no effect was produced with 2.5 mcg, then a further injection of 3.75 mcg was given on visit 3. If the desired effect was obtained with 3.75 mcg, without significant side-effects, then the injection was repeated at visit 4. If the first injection

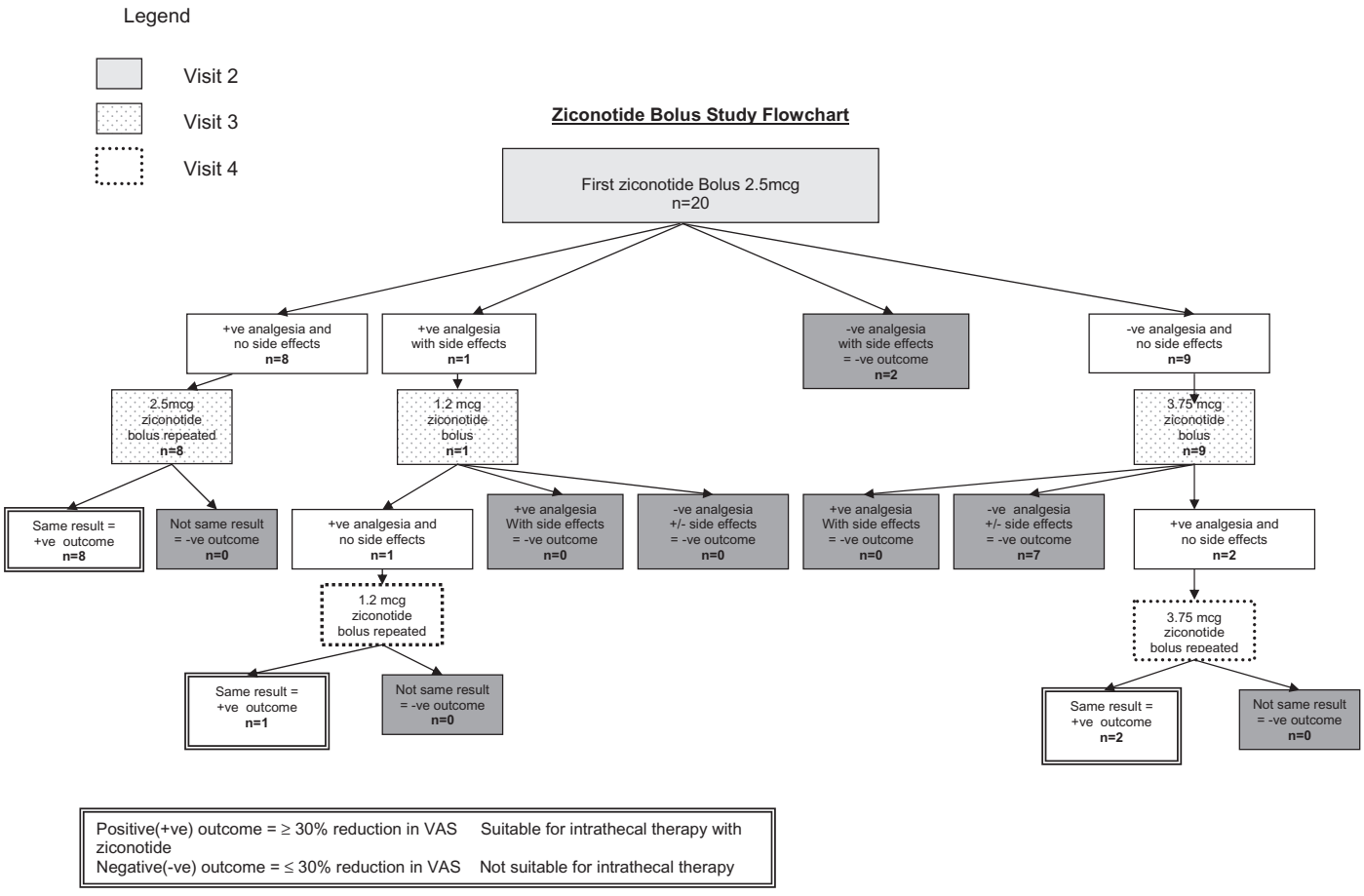

Figure 1. Ziconotide bolus study flowchart.

(2.5 mcg) produced a satisfactory response but intolerable side-effects, a dose of 1.2 mcg was administered on visit 3. If a good response, without significant side-effects, occurred with 1.2 mcg, then on visit 4, 1.2 mcg was given.

A successful trial was defined as a good analgesic response (≥30% reduction in baseline visual analog scale [VAS]) with no side-effects on two occasions. Treatment failure was defined as no analgesia or significant side-effects. Failure to reproduce analgesia and/or adverse effects on two occasions was also considered a treatment failure.

Data collection

At visit 1, informed consent, demographics, medical/pain history, pain and concomitant medications were noted. A physical examination was performed. CK was measured. A pain VAS, blood pressure, heart rate, and respiratory rate were recorded.

At visits 2, 3, and 4, the patient was admitted to the day unit for overnight stay. A brief physical examination was performed. A pain VAS and vital signs were recorded before bolus dosing and then every hour for six hours postbolus. Adverse events were documented with any changes in concomitant medications. On the following morning before discharge, a Mini Mental State Examination was performed. A telephone follow-up occurred on the same afternoon to record the pain VAS and any adverse events. Serum creatine kinase (CK) was repeated at the last visit.

Statistics

For primary analysis, a summary measures approach was adopted (15). For each patient, the arithmetic mean for both "usual and current" pain VAS score (mean of baseline visit score plus all prebolus scores: "pre-injection") and mean of all hourly "post-injection" pain VAS scores across one to three visits were calculated; that is, 6 to 18 repeated VAS ratings. These data were analyzed using a generalized estimating equations (GEE) model with a robust estimator of covariance, with mean pain VAS as the outcome and treatment (preinjection and postinjection) as the predictor. Sex, center, age, and pain etiology (neuropathic vs. "other") were included as factor covariates (age was constructed as a binary variable based on a median split of < or >49.8 years). To explore the potential generalizability of the treatment, interaction effects were inspected, with due caution, for any indication that the treatment effect might differ substantially by sex, center, age group, or pain etiology. The 100 mm VAS scale is strictly a percentage from 0 to 100 (or equivalently a proportion from 0 to 1); data were therefore modeled assuming a binomial distribution (events/trials: VAS score/100) with a logit link, providing the mean effect of treatment with its 95% confidence interval (CI). A responder analysis was conducted by deriving the proportion of patients experiencing a reduction in pain of ≥30% from preinjection to postinjection. The number needed to treat (NNT) was estimated as 1/the proportion of patients benefiting. The CI for the NNT was derived in the same fashion from the lower and upper limits of the CI for the proportion benefiting. In an exploratory secondary analysis, the trend in pain reduction across the six hours of measurement postinjection was examined. Data were analyzed using a GEE model with pain VAS as the outcome and time as the predictor (seven data points; preinjection and hourly from one to six h postinjection). Polynomial contrasts were used to evaluate the trend in pain VAS over time. All analyses were conducted using IBM SPSS Statistics 19.0 (IBM SPSS Statistics Inc., Chicago, IL, USA) and StatsDirect (Altrincham, UK; v. 2.7.8) software.

RESULTS

Twenty patients (12 female and 8 male) were recruited, ten at each of the two sites. Mean (standard deviation) age, height, and body mass were 50.8 (11.6) years, 1.67 (0.17) m, and 79.7 (20.6) kg, respectively. Pain types included failed back surgery syndrome ($N = 5$), neuropathic ($N = 9$), posttraumatic ($N = 3$), and degenerative ($N = 3$)(Fig. 2). (For the purposes of exploring the interaction of pain etiology with treatment, those patients with neuropathic pain were

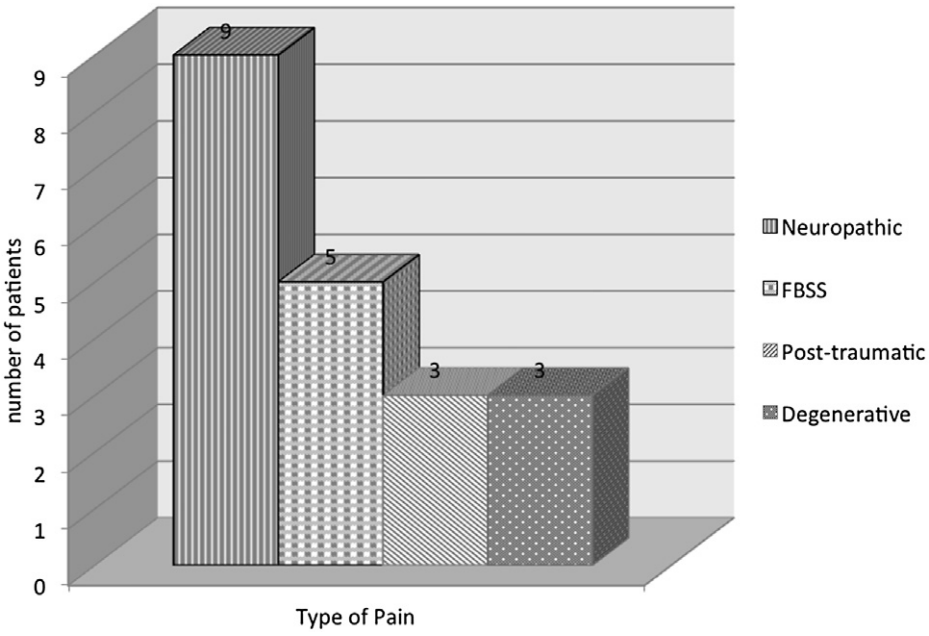

Figure 2. Graph illustrating number of patients with different types of pain.

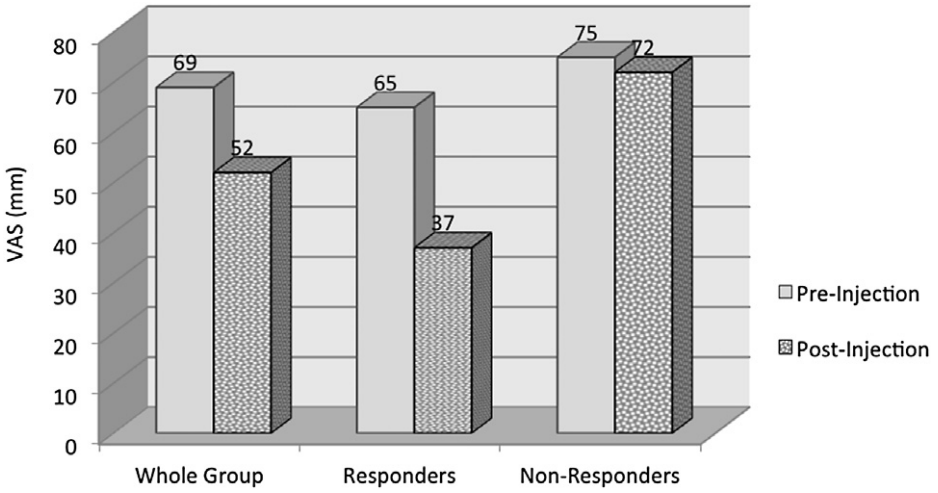

Figure 3. Graph illustrating the mean change in VAS in the preinjection trial and postinjection trial of the responder group and nonresponder group.

compared with all others.) The GEE analysis of summary measures showed that mean pain VAS reduced by 17 mm (95% CI, 10 to 23 mm) from preinjection (69 ± 23 mm) to postinjection (52 ± 25 mm). This effect represents a mean reduction in pain of approximately 25% at the group level. The treatment effect derived from a simple unadjusted analysis, with no covariates included, was identical on this occasion. The mean decrease in VAS in the "responder" group was 28 mm (95% CI, 22 to 34 mm). This effect represented a reduction from a mean of 65 mm to 37 mm (43%). The mean decrease in VAS in the nonresponder group was 3 mm (95% CI, −1 to 7 mm); there was a reduction from a mean of 75 to 72 mm (4%) (Fig. 3).

Interaction effects showed that the mean efficacy of the treatment did not appear to differ substantially by sex, center, age group, or pain etiology. For men, the effect of the treatment was a reduction in pain VAS of 19 mm and in women 15 mm (95% CI for the difference, −9 to 17 mm). The difference in the mean treatment effect between the two centers was 2 mm (reduction in pain VAS of 18 mm vs. 16 mm; 95% CI for the difference −12 to 16 mm). The reduction in pain VAS in the younger compared with older age group was 19 mm vs. 15 mm (95% CI for the difference, −10 to 18 mm). The mean treatment effect in those with neuropathic pain was 17 mm vs. 16 mm in the "other" group (95% CI for the difference −13 to 15 mm).

Of the 11 responders, seven underwent ITDD implant procedures, two withdrew because of adverse effects after their first bolus, one patient refused an implant, and one could not have an implant due to lack of funding. Of the seven patients who had an implant, three remain on ziconotide and four changed from ziconotide to other IT drug therapy. The proportion of the sample classified as responders to treatment was 0.55 (95% CI [Newcombe–Wilson method (16)], 0.34 to 0.74) (11/20 patients), providing an NNT of 2 (95% CI, two to three patients; all values rounded up to nearest whole number). Secondary analysis revealed a strong curvilinear (quadratic) trend, indicating that on average (at the group level), the majority of reduction in self-reported pain occurred by two hours postinjection (mean VAS 53 mm); thereafter, pain began to plateau (Fig. 4). Nine patients needed a second bolus of 3.75 mcg and eight patients received a second bolus of 2.5 mcg. Two patients withdrew after their initial bolus of 2.5 mcg due to serious adverse events. One patient had a second and third bolus dose of 1.2 mcg. Three patients had a third bolus. There were 76 adverse events; three were serious

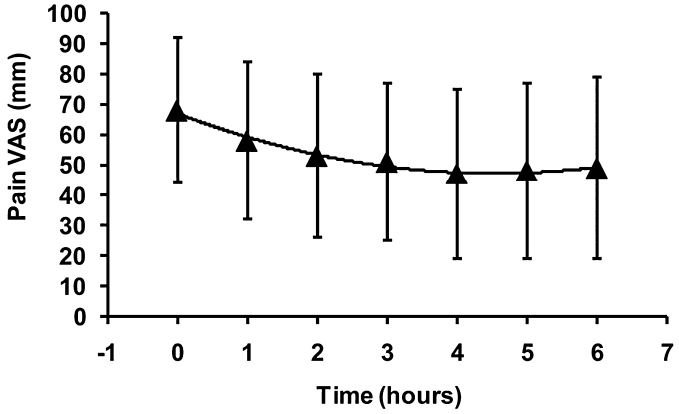

Figure 4. Mean (SD) pain VAS (mm) preinjection (zero hour) and hourly postinjection (one to six hours). The best-fit second-order polynomial curve is displayed ($Y = 0.964(X^2) - 8.75(X) + 67.14$; $R = 0.99$).

(Table 1); 14 of these events were unrelated to the study drug; no event required further action. Three serious adverse events occurred in three patients: one dizziness after 2.5 mcg; one double vision, depression, anxiousness, nausea, dizziness, and unsteadiness after 2.5 mcg; and one unrelated infected foot. There was a threefold increase in CK concentration in one patient; this continues to be monitored. Another patient had a significantly high CK before the bolus; this decreased at the last visit. One patient did not have a second CK measured as he withdrew from the trial. Another sample was not collected at the last visit due to error. Of the remaining 16 patients, there was no significant change in CK.

DISCUSSION

Ziconotide received regulatory approval for the treatment of intractable chronic pain as a continuous spinal infusion and not as a bolus dose. Even though our study was small, 55% of our patients had a positive response with a bolus. Mean VAS reduced by approximately 25% at the group level and the responder group demonstrated a mean pain reduction of more than 40%. The NNT for benefit was 2. However, a dose increase did not necessarily result in increased

Table 1. Total Number of Adverse Events Reported During the Ziconotide Bolus Trial.

System	Event	Total # reported	Dose of ziconotide		
			1.25 mcg	2.5 mcg	3.75 mcg
CNS	Dizziness	11	1	10	
	Nystagmus	1		1	
	Altered speech	1		1	
	Double vision	5		3	2
	Confusion	1		1	
	Drowsiness	4	1	3	
	Lightheadedness	4		2	2
	Depression	1		1	
	Headache	3		2	1
	Anxious	1		1	
CNS other	Pressure on top of head	1			1
	Pain around injection site	4		1	3
	Backache	1			1
	Increased body pain	2			2
	Generalized body pain	2		2	
	Increased spinal pain	1		1	
	Tired	1			1
	Leg weakness	1			1
	Vacant feeling	1		1	
	Unsteady on feet	1		1	
	Bilateral paraesthesia of feet	1		1	
	Hot sensation both shoulders	2		1	1
	Intermittent right leg weakness	1			1
	Pain on mobilizing	1			1
CVS	Hypotension	5		5	
RS	Bradypnea	1		1	
	Decreased oxygen saturation	1		1	
GIT	Nausea	7		4	3
	Diarrhea	1		1	
	Vomiting	1		1	
Urinary	Urinary incontinence	1		1	
	Lack of bladder sensation	2		2	
Miscellaneous	Infected toe nail	1		1	
	Infected sinus foot	1		1	
	Facial flushing	1		1	
	Feeling cold	1		1	
	Appendectomy	1		1	

CNS, central nervous system; CVS, cardiovascular system; GIT, gastrointestinal tract; RS, respiratory system.

response; only two of our subjects reported a positive response with a dose increase to 3.75 mcg and one reported a positive response with a dose decrease to 1.2 mcg. Only 2 of our 20 patients had serious ziconotide-related adverse events (these occurred at 2.5 mcg). A significant number of adverse events were reported that did not require intervention; many of these are in the summary of product characteristics and were expected.

The safety and efficacy of IT ziconotide were demonstrated in three double blind studies using infusions (4–6). The participants had long-standing nonmalignant chronic pain that was unresponsive to conventional pain management. Grigsby (13) reported a similar open-label bolus study. Single boluses of ziconotide 1, 3, and 5 mcg were administered; patients could then opt to have continuous IT ziconotide added to their regimen. Participants were asked to note pain scores for 24 hours after the bolus and to complete a patient satisfaction questionnaire. At 24 hours after the trial, patients could opt for a higher dose single bolus, withdraw, or add IT ziconotide to their treatment. Once a continuous infusion was commenced, efficacy and adverse events were monitored for six months. Forty-two patients enrolled, but 12 were ineligible for the bolus trial. Thirty patients received the first bolus of 1 mcg; their numerical rating score was reduced by 29% at one hour and 17% at 24 hours. Six patients discontinued; 14 added IT ziconotide to their treatment (1 mcg group). Ten patients received the next dose of 3 mcg; their mean numerical rating score was reduced by 20% at one hour and 24 hours; three of this group discontinued and four added IT ziconotide to their treatment. Three patients received the 5 mcg dose. The most common adverse events after a bolus that resulted in discontinuation were nausea and vomiting as in our study. This study showed that an increase in the bolus dose did not necessarily give an increased response; there was also no relationship between the successful trial dose and the long-term infusion dose. Rosenblum (14) conducted a small multidose placebo controlled study in six patients with chronic pain (four patients with failed back surgery syndrome, one with erythromelalgia, and one with spinal cord injury). Patients received a dose of ziconotide 0, 2, 4, or 8 mcg in a randomized sequence. Conversely, increasing the dose of ziconotide generally resulted in increased analgesia. The

proportion of >50% positive responders was 0% for 0 mcg, 17% for 2 mcg, 25% for 4 mcg, and 50% for 8 mcg. While no serious adverse events were reported, 66% had nausea and/or dizziness at 8 mcg; 33% had nausea and vomiting at 4 mcg; 66% had ataxia after 8 mcg. In a small study by Okano et al. (12), 11 patients with IT pumps received single boluses of ziconotide 5 mcg, 2.4 mcg, and 1.2 mcg. Almost 73% of patients reported significant pain relief (>50% reduction from preprocedure level). Serious adverse events were urinary retention, hallucinations, and motor weakness, each occurring in one patient.

These three studies and our study show that bolus administration of ziconotide is safe and effective in predicting response to ziconotide infusion. It is generally agreed that a trial should be performed prior to implant (11). However, there is no consensus about the type of trial that should be used. Single bolus injections offer the advantage of being simple and are associated with a low risk of infection compared with almost 7% reported for an infusion (6,11). Bolus administration and assessment require a shorter duration of hospitalization and thus causing less disruption for patients who need an overnight stay rather than admission for a week or longer for a traditional trial. One significant benefit is the lower cost of this decreased hospital stay. Anderson et al. reported a reduction of cost by almost three times with IT injections as opposed to continuous infusion ($1900 for IT injection vs. $4800 for continuous infusion) (17). The risk of postdural puncture headache is less with a bolus (0–10%) than with an infusion (13%) (18). One disadvantage of a bolus injection is the potential for a high placebo response; a continuous infusion may be associated with a smaller placebo response. In addition, an infusion may better mimic the slow and progressive titration effects of a chronic drug infusion (11). Slow titration may clarify the starting dose for a continuous IT infusion after implantation (17). In a focused review of methods for ziconotide trialing (19), the authors concluded that no trialing method had been shown to be superior when comparing a continuous infusion, a limited duration infusion, or a bolus injection. However, a survey showed that most pain physicians preferred to use a continuous infusion to select patients for permanent implants (10,18); respondents thought that this was closer to an infusion from a pump—this is intuitive rather than evidence based.

Finally, our study has many limitations, including small numbers, lack of blinding, and no placebo or active control group. It is important to note that the NNT we have derived is exploratory; it might be an underestimate of the NNT that could be observed in a subsequent randomized controlled trial. Clearly, further appropriately powered, double blind, randomized controlled trials are required to establish the role of trialing ziconotide by bolus.

Authorship Statement

All the authors took part in the work. E Buchser, C Perruchoud, S. Eldabe, K.H. Simpson, and A.M. Batterham conceived the study design. S. Eldabe and K.H. Simpson led the patient care and recruitment. M. Brookes, H. Radford, G. Madzinga, and T. Crowther led the regulatory aspects and all data collection for the study. A. Gulve and G. Baranidharan contributed to patient care and recruitment. A.M. Batterham conducted the statistical analysis. S.I. Mohammed, S. Eldabe, K.H. Simpson led the writing of the manuscript, with contribution comments from the other authors. All authors above contributed to the drafting and critical appraisal of the manuscript.

Funding Disclosure

We declare that the study was funded entirely by Eisai Europe, but sponsored and conducted independently by the investigators K.H. Simpson and S. Eldabe and their organizations.

How to Cite this Article:

Mohammed S.I., Eldabe S., Simpson K.H., Brookes M., Madzinga G., Gulve A., Baranidharan G., Radford H., Crowther T., Buchser E., Perruchoud C., Batterham A.M. Bolus Intrathecal Injection of Ziconotide (Prialt®) to Evaluate the Option of Continuous Administration via an Implanted Intrathecal Drug Delivery (ITDD) System: A Pilot Study.
Neuromodulation 2012; e-pub ahead of print. DOI: 10.1111/ner.12003

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