Accuracy and Effectiveness of Morphine Sulfate Infusion via the Prometra® Programmable Intrathecal Infusion Pump

Timothy Deer, MD, Steven Rosen, MD, Elmer Dunbar, MD, John Barsa, MD,
Gurpreet Padda, MD, Gopala Dwarakanath, MD and Richard Rauck, MD

INTRODUCTION

This presentation is focused on the **long-term results** of a pivotal trial examining the accuracy and effectiveness of a new third generation programmable pump system called Prometra. Intrathecal infusion pumps are increasingly used to deliver analgesics for chronic intractable pain and the accuracy of the drug delivered by the pump is a very important therapeutic component. Currently, market-approved intrathecal drug delivery systems are labeled ± 14.5% for accuracy.

Device Description

The Prometra Programmable Pump, developed by InSet Technologies Incorporated (Mt. Olive, NJ) is a pressure-driven, calibrated, microdosing pump. This type of design is expected to provide a number of improvements over older generations of programmable pumps, including:

- Non-compliant dosing chamber that provides meticulous measurement (no rollers)
- Precise, controlled drug flow with electronic dual gated system
- A reservoir that acts as a volume-control regulator in micro increments
- An isolated valve system robust to temperature and pressure changes
- Ability to completely shut down (zero flow)

In addition to improved accuracy, it is expected to have microvolume delivery capability, a long device life (due to few moving parts and energy-efficient design), relative light weight, and the ability to deliver advanced compounds, such as large proteins.

METHODS

Protocol Design

The PUMP study is a prospective, multi-center, open-label evaluation of the Prometra Programmable Pump System in the administration of intrathecal morphine sulfate for the treatment of chronic intractable pain.

Seven centers participated in this study which began enrollment in March 2007 and finished in December 2007 (Table 1). One hundred and ten (110) patients met inclusion criteria and were implanted with the Prometra Pump.

Table 1: Enrollment by Clinical Site

Institution	Location	Investigators	Number of Patients Enrolled
Center for Interventional Pain Management	St. Louis, MO	Gurpreet Padda	31
Pain Institute of Tampa	Tampa, FL	John Barsa	20
Fox Chase Pain Management Associates	Jenkintown, PA	Steven Rosen	17
Center for Clinical Research	Winston-Salem, NC	Richard Rauck	16
Center for Pain Relief	Charleston, WV	Timothy Deer	16
Pain Control Network	Louisville, KY	Elmer Dunbar	7
Lowell General Hospital	Lowell, MA	Gopala Dwarakanath	3
		Total 110	

Upon implantation (Day 0), the pump was filled with an appropriate concentration of preservative-free morphine sulfate and programmed for constant flow. Daily dose was based on patient need and could be adjusted at any time throughout the course of the study. Patients attended follow-up visits at Day 10 (±5 days) to assess wound healing, and then monthly (±7 days) up to 6 months post-implantation to assess device performance, and refill the reservoir. During refill visits, the volume of residual drug in the pump was measured using the volumetric refill syringe supplied with the device, and the delivered volume was calculated. After 6 months, patients entered the long-term phase of the study with visits scheduled every 3 months (±30 days). Data is managed and analyzed by an independent third party (inVentiv Clinical Solutions, The Woodlands, TX).

Endpoints and Analysis

The primary endpoint is the accuracy of medication delivered. **This was measured by comparing the volume of medicine programmed for delivery with the amount actually delivered.** Pump refills were required monthly for the first six months post-implantation and then quarterly until the device receives market-approval. Additional refills were allowed as needed to avoid interruption of therapy. Accuracy was measured using 1,098 refill visits from 107 patients.

The secondary endpoint addressed the efficacy of treatment, as measured by changes from baseline in three pain and quality of life assessments, the NRS, VAS, and ODI.

- *The Visual Analog Scale (VAS)* is a 100-mm line, with 0 indicating no pain and 100 indicating the worst imaginable pain. The patient marks the line at a point that indicates their current level of pain.
- *The Numeric Rating Scale (NRS)* is an 11-point pain scale (0-10), with 0 meaning no pain and 10 meaning the worst imaginable pain. The patient chooses a value that best describes their average pain in the previous 24 hours.
- *The Oswestry Disability Index (ODI)* is a patient-completed questionnaire that gives a subjective percentage score of level of disability in activities of daily living (ADLs). Each activity is rated on a scale of 0 (no pain /limitations) to 5 (extreme pain/limitations). The index is calculated as: ODI (%) = (Total Score / 5 x Number of Activities Assessed) x 100

RESULTS

Patient Demographics

The data represented here reflects data collected through April 15, 2009. To date, total device exposure is 59,491 days (approx. 163 patient years). Baseline demographics of the patient population are provided in Table 2 and were similar to other published studies involving implantable drug delivery systems (IDDSs).[4-7] The ratio of male to female patient enrollment is reflective of the type and frequency of intractable back pain and its underlying distribution in the general population.

Table 2: Demographics (N = 110)

Demographic	Result
Gender - N (%)	
Male	59 (54%)
Female	51 (46%)
Age - (years)	
N	110
Mean	56
SD	13
Median	55
Range	28-84

The mean duration of pain at baseline was 12.4 ± 9.7 years (range <1-52 years). The majority of patients reported only neuropathic pain; the most common causes of pain were post-lumbar spine surgery and intractable back pain (Table 3).

Table 3: Pain History of Enrolled Patients (N = 110)

Pain Category	N (%)
Neuropathic	64 (58%)
Nociceptive	12 (11%)
Both	34 (31%)
Pain Etiology[a]	**N (%)**
Post-Lumbar Spine Surgery with Pain	60 (55%)
Intractable Back Pain	57 (52%)
Arachnoiditis	26 (24%)
Chronic Regional Pain Syndrome	24 (22%)
Post-Cervical Spine Surgery with Pain	14 (13%)
Vertebral Body Compression Fractures	6 (6%)
Post-Thoracotomy Pain Syndrome	3 (3%)
Cancer Pain	3 (3%)
Phantom Limb Pain	0 (0%)
Other	70 (64%)

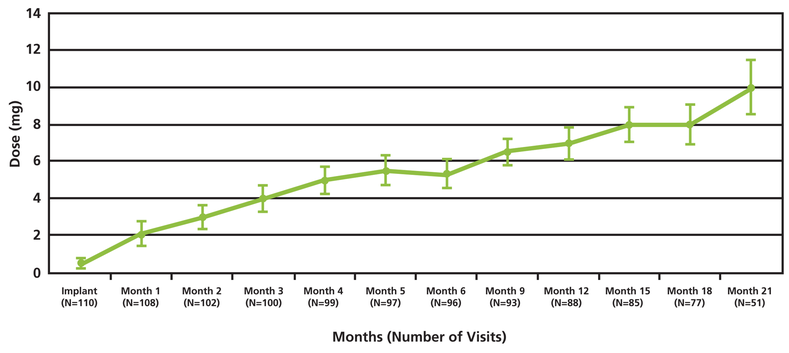
[a] Percentages total >100% because patients reported multiple causes and types of pain.

Compliance with the follow-up schedule was high, with 95% of monthly visits completed inside the protocol specified windows.

Morphine Dose

The median programmed morphine dose is presented in Figure 1. The increase in median dose from the time of implant is consistent with previous studies.[1,2]

Figure 1: Median Dose (mg) by Visit



Accuracy

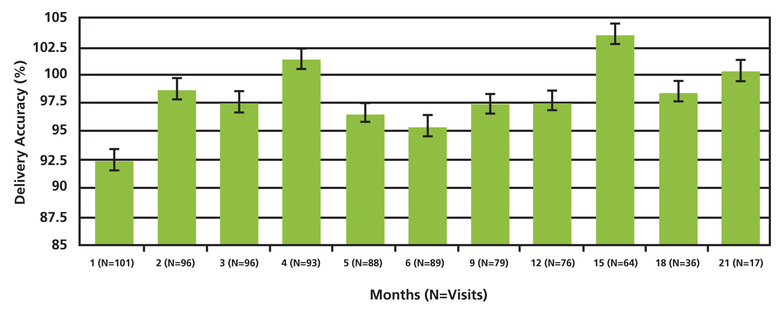
The mean accuracy of refill visits (N = 1098) was 97.4%, with a 90% confidence interval of 96.8% – 98.0% (Table 4).

Table 4: Accuracy of Drug Delivery

Medication Delivered	Population
N (visits)	1098
Mean (% ±SD)	97.4 ±3.8
Range (%)	81.8 – 107.7
90% confidence interval of mean (%)	96.8 – 98.0

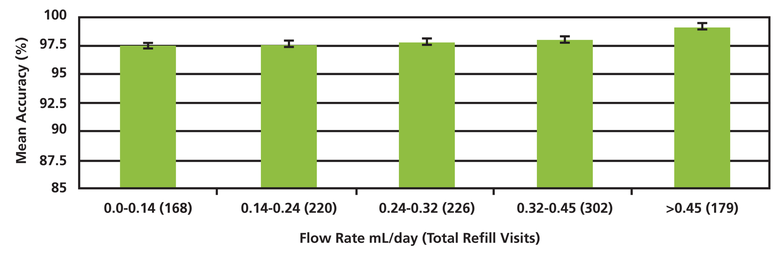
Accuracy remained consistent throughout the study (Figure 2). Statistically significant differences ($p \leq 0.05$) were observed between Month 1 and Months 2, 3, 4, 9, 12, and 15, between Month 4 and Month 6, and between Month 15 and Months 3, 5, 6, and 9. However, the mean accuracy for each month was well within the target endpoint of 85% – 115% accuracy.

Figure 2: Drug Delivery Accuracy by Month



To examine accuracy as a function of daily flow rate, programmed flow rates were divided into five groups with comparable numbers of visits (Figure 3). No significant differences were seen between flow rate groups ($p > 0.05$).

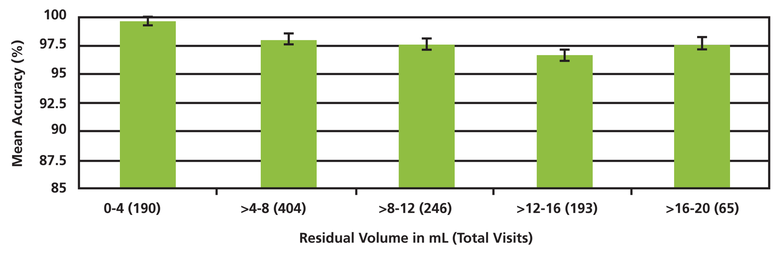
Figure 3: Mean Accuracy vs. Flow Rate



Finally, accuracy was consistent as a function of residual volume (Figure 4). No significant differences were seen between residual volume categories ($p \geq 0.05$). Notably, accuracy was consistently high in the highest residual volume category (>16-20 mL).

RESULTS

Figure 4: Mean Accuracy vs. Residual Volume



Efficacy

When compared to baseline there were statistically significant decreases in mean pain and disability scores at all visits. 84% of patients reported improvements in VAS scores, 76% in NRS, and 68% in ODI scores (Table 5). A negative change in scores indicates an improvement in pain or disability.

Table 5: Improvements in Pain and Disability Scores

Visit	N	Raw score (mean ± SD)	Range	% Change (mean ± SD)	*p* value
VAS					
Baseline	102	71.7 ± 16.6	35 – 100		
Month 6	83	50.9 ± 25.3	1 – 100	-28.4 ± 34.7	<0.05
Month 12	62	49.9 ± 22.7	0 – 100	-27.7 ± 32.1	<0.05
NRS					
Baseline	102	7.5 ± 1.5	4 – 10		
Month 6	83	5.5 ± 2.2	0 – 10	-26.2 ± 28.2	<0.05
Month 12	62	5.5 ± 2.1	2 – 10	-25.0 ± 26.4	<0.05
ODI					
Baseline	102	57.1 ± 14.3	14.0 – 95.6		
Month 6	83	49.9 ± 17.6	4.0 – 86.0	-10.0 ± 26.6	<0.05
Month 12	62	46.8 ± 16.3	4.0 – 84.0	-13.5 ± 27.9	<0.05

In addition to the accuracy and efficacy data, the Prometra system provided safe therapy in this patient population. No unanticipated adverse events or deaths were attributed to the device or the procedure, and no pump failures were reported during the study. There have been no reports of neuro-toxicological effects or symptomatic granuloma formation in this pivotal clinical study, which has recently surpassed two (2) years of investigational experience. The adverse events and device-related complications reported were consistent with complications described in other studies involving IDDSs.[5-9, 13-17]

DISCUSSION

In the current study, the Prometra system has been shown to deliver the programmed drug volume with an improved level of accuracy (mean accuracy 97.4%, with a 90% confidence interval of 96.8% – 98.0%). Compared to current market-approved pumps, this is significantly higher. **Accuracy is consistent over the 21-month period of the study, and was not significantly affected by flow rate or residual drug volume.** The consistently accurate drug delivery at residual volumes under 2 mL suggests the potential for improved outcomes over currently marketed pumps, which recommend refills before the reservoir reaches such low volumes.[7, 9, 10]

Highly accurate dosing intuitively offers clinical benefits for patients with greater sensitivity to or side effects from morphine treatment. Higher accuracy will improve outcomes when using drugs with higher potency or more narrow therapeutic windows, and may facilitate the clinical use and optimization of drug admixtures for particular pain conditions or patient subpopulations. It is unclear whether increased drug accuracy might also reduce the risk of granuloma formation, a phenomenon that is poorly understood but may be linked to drug concentration and dose.[4, 13, 14]

CONCLUSION

The Prometra Programmable Pump System has been shown to provide consistently accurate drug delivery (average error ±3% of programmed volume), and to provide effective therapy for the patient population over a 21-month period. The design of the system offers several characteristics not available in current market-approved IDDSs. This system may offer more reliable analgesia with fewer side effects, a longer device life (noncompliant titanium chamber; fewer moving parts), as well as opportunities to further optimize approaches used in the treatment of chronic pain by intrathecal infusion.

REFERENCES

[1]Onofrio BM, Yaksh TL. Long-term Pain Relief Produced by Intrathecal Morphine Infusion in 53 Patients. *Journal of Neurosurgery* 72:200-209, 1990.

[2]Paice JA, Penn RD. Intraspinal Morhpine for Chronic Pain: A Retrospective, Multicenter Study. *Journal of Pain and Symptom Management* 11(2): 71-80, 1996.

[3]Smith HS, Deer TR, Staats PS, Singh V, Sehgal N, Cordner H. Intrathecal drug delivery. *Pain Physician* 2008; 11:S89-S104.

[4]Paice JA, Penn RD, Shott S. Intraspinal morphine for chronic pain: A retrospective, multicenter study. *J Pain Symptom Manage* 1996; 11:71-80.

[5]Winkelmuller M, Winkelmuller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. *J Neurosurg* 1996; 85:458-467.

[6]Medtronic® IsoMed® Constant Flow Infusion: Summary of Safety and Effectiveness Data. 2000. U.S. Food and Drug Administration. http://www.fda.gov/cdrh/pdf/p990034.html.

[7]Deer T, Chapple I, Classen A, Javery K, Stoker V, Tonder L, et al. Intrathecal drug delivery for treatment of chronic low back pain: Report from the National Outcomes Registry for Low Back Pain. *Pain Med* 2004; 5:6-13.

[8]Rigoli G, Terrini G, Cordioli Z. Intrathecal baclofen withdrawal syndrome caused by low residual volume in the pump reservoir: A report of 2 cases. *Arch Phys Med Rehabil* 2004; 85:2064-2066.

[9]Taha J, Favre J, Janszen M, Galarza M, Taha A. Correlation between withdrawal symptoms and medication pump residual volume in patients with implantable SynchroMed pumps. *Neurosurgery* 2004; 55:390-393.

[10]Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ. Inflammatory masses associated with intrathecal drug infusion: A review of preclinical evidence and human data. *Pain Med* 2002; 3:300-312.

[11]Allen JW, Horais KA, Tozier NA, Wegner K, Corbeil JA, Mattrey RF, Rossi SS, Yaksh TL. Time course and role of morphine dose and concentration in intrathecal granuloma formation in dogs: A combined magnetic resonance imaging and histopathology investigation. *Anesthesiology* 2006; 105:581-589.

[12]Follett KA, Naumann CP. A prospective study of catheter-related complications of intrathecal drug delivery systems. *J Pain Symptom Manage* 2000; 19:209-215.

[13]Turner JA, Sears JM, Loeser JD. Programmable intrathecal opioid delivery systems for chronic noncancer pain: A systematic review of effectiveness and complications. *Clin J Pain* 2007; 23:180-194.

[14]Ethans KD, Schryvers OI, Nance PW, Casey AR. Intrathecal drug therapy using the Codman Model 3000 Constant Flow Implantable Infusion Pumps: Experience with 17 cases. *Spinal Cord* 2005; 43:214-218.

[15]Cohen SP, Dragovich A. Intrathecal analgesia. *Med Clin N Am* 2007; 91:251-270.

[16]Guillaume D, Van Havenbergh A, Vloeberghs M, Vidal J, Roeste G. A clinical study of intrathecal baclofen using a programmable pump for intractable spasticity. *Arch Phys Med Rehabil* 2005; 86:2165-2171.

[17]Koulousakis A, Kuchta J. Intrathecal antispastic drug application with implantable pumps: Results of a 10-year follow-up study. *Acta Neurochir Suppl* 2007; 97:181-184.

This study was sponsored and funded by InSet Technologies.
CAUTION: Investigational Device. Limited by Federal (or United States) Law to Investigational Use.