Clinical Accuracy and Safety Using the SynchroMed II Intrathecal Drug Infusion Pump

Kelly Wesemann, MS,* Robert J. Coffey, MD,* Mark S. Wallace, MD,† Ye Tan, MS,* Steven Broste, MS,* and Asokumar Buvanendran, MD‡

Background and Objectives: We evaluated the infusion accuracy and device-related safety of implantable drug infusion pumps in subjects with chronic pain or severe spasticity.

Methods: Nine centers in the United States enrolled patients receiving intrathecal drug delivery systems to manage chronic pain and/or severe spasticity. Infusion accuracy was assessed at 6 and 12 months by comparing syringe-measured volumes to programmer-predicted volumes. Safety was evaluated through analysis of adverse events. Separate laboratory testing conducted by the manufacturer also evaluated infusion accuracy.

Results: Eighty of 82 enrolled subjects were implanted. Sixty-five and 54 subjects, respectively, were analyzable for accuracy at 6 and 12 months. On average at 6 months, the pumps were measured to have delivered 1% more than the programmed delivery volume. Analyzed on a per-refill basis, the pumps delivered, on average, 2.5% more than the programmed delivery volume. Differences between per-refill means versus per-subject cumulative means were due to limitations in clinicians’ ability to precisely visualize small single syringe-volume differences, or possibly incomplete withdrawal of fluid from the pump. Laboratory testing demonstrated a per-refill mean accuracy error of minus 2.4%. Because average observed flow-rate error at 6 and 12 months (1% overinfusion) was derived from pump residual volume measurements by syringe and carried out in a clinical setting, clinical volume ratios were larger than direct volume measurements by weight observed in the laboratory. No deaths, permanent injuries, or unanticipated adverse device effects occurred.

Conclusions: The pump accurately delivered intrathecal medication in the clinical setting of this study. Adverse events were similar in nature and severity to those described in the product labeling and literature.

From the *Medtronic, Inc, Minneapolis, MN; †University of California San Diego, La Jolla, CA; and ‡Rush University Medical Center, Chicago, IL. Accepted for publication April 9, 2014.

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METHODS

The US Food and Drug Administration and institutional review boards approved the clinical investigational plan before study initiation. All patients or their legal guardians provided written informed consent. The trial was sponsored by the manufacturer and registered as NCT00773019 at clinicaltrials.gov on August 21, 2008. The study was conducted using commercially available pumps and refill kits as a condition of approval required by the US Food and Drug Administration.

Devices under study were the SynchroMed II Model 8637 20- and 40-mL pumps (Medtronic, Inc, Minneapolis, Minnesota). Eligible subjects were at least 18 years old, were willing to return for follow-up visits, met labeled indications with no contraindications, and received their initial or replacement system for infusion of intrathecal medication to treat severe spasticity or chronic pain. Subjects who received a replacement system were allowed to use their existing catheter or have a new one implanted at the time of pump replacement surgery. Subjects were excluded if they had an ongoing infection, insufficient body mass to accept the pump, a condition in which the pump could not be implanted, a condition in which the pump could not be implanted close enough to the skin surface to ensure proper telemetry communication, or a life expectancy shorter than 1 year. Subjects were required to return for refill visits (at minimum) at 1, 6, and 12 months after implantation. If additional refills were needed, data from those visits also were collected. Each site’s principal
investigator was a physician responsible for all study activities who ensured that any delegated study-specific activities were performed by individuals qualified by education and training. Pump flow rates and drug dosages were prescribed by the study physicians and allowed to be changed as needed to meet therapeutic needs. Adverse events (AEs) were assessed at all scheduled and unscheduled visits.

**Accuracy**

Drug residual volumes were obtained using the syringe supplied in the commercially available refill kit. The primary outcome variable was each subject’s cumulative 6-month accuracy ratio, calculated as the ratio of the aggregate clinic-measured volume of drug dispensed divided by the aggregate pump calculated volume dispensed over the consecutive refill sessions through 6 months (Eq. 1). Accuracy ratios were also calculated through 12 months.

\[
\text{Eq. 1. Primary End Point: Per Subject Accuracy Ratio at 6 Months} \\
\text{Per subject ratio} = \frac{\text{Total clinic measured volume dispensed}}{\text{Total pump calculated volume dispensed}} \\
\text{CMV}_{1} + \text{CMV}_{2} + \text{CMV}_{3} \\
\text{PCV}_{1} + \text{PCV}_{2} + \text{PCV}_{3} \\
\text{where x is the visit number}
\]

The end point required that more than 90% of subjects have an accuracy ratio between 0.75 and 1.25. Using a 1-sample binomial test with \( p_{0} = 0.1 \) versus \( p_{1} = 0.025 \), a 1-sided significance level of 0.05 and at least 80% power, a minimum sample size of 61 subjects was required. An accuracy ratio of 1.00 would indicate that the observed (clinic-measured) volume dispensed matched the pump-calculated volume exactly and would correspond to a 100% measured-to-calculated ratio and a 0% flow-rate error. Using the same 6-month dataset, an additional per-refill analysis was carried out on the clinic data using Eq. 2.

\[
\text{Eq. 2. Additional Analysis: Per-Refill Accuracy Ratio} \\
\text{Per refill ratio} = \frac{\text{Clinic measured volume dispensed visit x}}{\text{Pump calculated volume dispensed visit x}}
\]

Laboratory testing of 23 separate SynchroMed II pumps for 4 consecutive days compared the actual output compared with the pump calculated output using Eq. 3, at various infusion rates (0.1, 0.3, 0.5, and 0.7 mL/d) and reservoir volumes (full, half-full, and low [1–2 mL residual volume]). A mix of 20- and 40-mL pumps were tested at body temperature (37°C ± 1°C) using an analytical balance (Model HM-300, A&D Company, Tokyo, Japan) which measures to 0.0001 g to determine the infused volume of sterile water for injection by weight.

\[
\text{Eq. 3. Laboratory Testing: Accuracy Error} \\
\text{In vitro accuracy error (\%)} = \frac{\text{Measured flow rate-programmed flow rate}}{\text{Programmed flow rate}} \times 100
\]

**Safety**

Investigators reported all AEs during the 12-month study, categorizing each as either device system related or non-system related. System-related AEs included those related to the pump, catheter, incisional sites, programming/refill procedures, or surgery/anesthesia. Non-system-related events included those related to the intrathecal drug(s), concomitant medications, and new illnesses or worsening of preexisting conditions. An AE was categorized as serious if it resulted in inpatient hospitalization, prolongation of existing hospitalization, a life-threatening situation (immediate risk of death), persistent or significant disability or incapacity, permanent impairment of body function or permanent damage to a body structure, necessity for medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, patient death, or a congenital anomaly/birth defect. Terms were standardized using MedDRA (Medical Dictionary for Regulatory Activities Maintenance, version 8.0, Maintenance and Support Services Organization [MSSO], McLean, VA).

**RESULTS**

Eighty-two patients were enrolled from December 22, 2004, to November 7, 2007. Two subjects discontinued before device implantation, resulting in 80 SynchroMed II infusion pumps implanted at 9 investigational centers (41 receiving 20-mL pumps and 39 receiving 40-mL pumps). Mean subject age was 51.4 years (range, 22–89 years); 44 were male (55%), and 36 were female (45%). Forty-three subjects were being treated for spasticity, 32 for pain, and 5 were treated with intrathecal drugs for both spasticity and pain. Twelve subjects (15%) discontinued participation in the study prior to the 12-month visit. Figure 1 summarizes study compliance and the reasons for subject discontinuation prior to the 12-month visit.

**Flow-Rate Accuracy**

Seventy-four subjects completed the 6-month visit, with 65 subjects having sufficient data (193 refills in 65 subjects) for the primary analysis. The mean flow rate for subjects in the primary analysis data set was 0.330 mL/d, with a minimum of 0.048 and maximum of 1.959 (2 of 65 subjects were on flex dosing, and their flow rate was not calculated for this statistic). To be included in the primary analysis, subjects underwent at least 2 refills with no missing refill data elements. Among subjects with incomplete data sets, 2 subjects missed 1 visit each, and 7 who attended all visits were missing a critical data element. A summary of the 6-month per-subject clinical accuracy ratios appears in Figure 2. All ratios were within 0.75 to 1.25 and met the primary success criterion. The mean per-subject accuracy ratio for the
65 subjects was 1.01 (SD, 0.05; 101% of the programmed volume) for a plus 1% error at 6 months. The 12-month results in 54 subjects with complete data were similar. Accuracy ratios relatively far from the 1.01 mean (or 1.00 median) tended to be associated with relatively small total delivery volumes—a situation that can magnify otherwise small visual (syringe) measurement errors or variations.

Because the per-subject accuracy ratios combine data from multiple visits, an additional analysis was conducted to examine the refill ratio at each visit. Figure 3 illustrates the complete per-refill data, with the accompanying table showing calculations with and without the 4 outlier values (open boxes). The mean per-refill accuracy ratio without outliers was 1.025 (SD, 0.121; mean error of plus 2.5% overinfusion) in 189 refills at varying intervals and volumes. The mean per-refill accuracy is very similar to the mean per-subject accuracy, but there is a wider range and larger SD associated with these single observations. As illustrated in Figure 3, more discrepant accuracy ratios are seen in cases where smaller volumes were dispensed—a situation where small measurement variations or errors can be greater than the volume of drug that was delivered and magnify otherwise small visual (syringe) measurement errors or variations. Incomplete medication removal from the pump may provide an additional explanation of discrepant ratios, particularly those greater than 1.

Laboratory testing of 23 pumps over 92 refill cycles demonstrated an average flow-rate accuracy of 0.976 (SD, 0.019 (97.6% of the programmed volume; minus 2.4% average delivery error).

### Safety

Fifty-eight system-related AEs were reported in 38 (48%) of the 80 implanted subjects. These events were attributed to the pump, catheter, implant sites, the implant procedure, and programming. Table 1 summarizes system-related AEs in order of frequency. Most events resolved without hospitalization or surgical intervention. Thirteen subjects experienced system-related events that met serious criteria that were resolved through surgical intervention on the catheter or pump or medical intervention involving hospitalization. No deaths or permanent injuries occurred.

One possibly pump-related event demonstrates the importance of dose titration with a replacement pump. A subject entering the study received her study pump as a replacement for a previous pump. For some time prior to pump replacement, the patient had experienced symptoms consistent with loss of intrathecal baclofen effects. Oral baclofen relieved her symptoms and observed (old) pump residual volumes matched programmer expected volumes. The old pump (6 years old; SynchroMed EL) was replaced. Review of the operative report and programming
printouts reveal that intraoperative priming bolus may have caused 0.169 mL of drug (338 μg of Lioresal) to be administered uninten-
tionally. In addition, the new pump was programmed to the same

dose as the previous pump. Initially, the subject’s symptoms were

thought to be related to anesthesia. However, after the subject
return 4 days postoperatively with ongoing nausea, vomiting,

sedation, and lethargy, sequential decreases in the daily intrathe-

cal baclofen dosage led to symptom resolution (1113.1 μg/d to

849.3 μg/d). No further AEs occurred in this subject.

Three events resulted in pump explant. One event (catheter
break/cut) was experienced in a subject whose repeated with-
drawal symptoms led to system replacement. At the time of reop-
eration, a leak in the catheter was discovered so the catheter was
repaired, and the pump was replaced at the physician’s discretion.

The second event (implant site infection) was an infection
detected at 167 days after implantation that led to system removal.
Both pumps were returned to the manufacturer, and no defect
was found. The third event of repeated drug withdrawal symptoms
(drug withdrawal syndrome) was experienced in a subject re-
ceiving intrathecal morphine for pain. Although investigations
revealed no evidence of device system malfunction, the subject
underwent complete infusion system explantation and replace-
ment (per-refill volume ratios were 1.0–1.08, indicating no underin-
duction). The explanted pump in question was lost in transit upon
attempted return to the manufacturer and could not be analyzed.

Sixty-six events reported in 32 subjects (40%) were related
to intrathecal or nonintrathecal drugs. None of these events re-
sulted in surgical intervention on the drug infusion system and

were most often treated by adjusting intrathecal or nonintrathecal

medications.

**DISCUSSION**

**Flow-Rate Accuracy and Patient Safety**

Pump accuracy analyses in the clinical setting, as performed
in this study, reflect factors that influence the actual flow rate
(temperature, atmospheric pressure, fullness of the reservoir) as
well as those that influence flow-rate calculations during a single
visit (limitations of visual perception of small syringe volume
differences, incomplete withdrawal of fluid from the pump, unde-
tected partial pocket fill at previous visit, motor stall, or catheter
obstruction). Having a cumulative aggregate volume calculation
based on multiple refills of each pump as the primary end point
reduced the effects of perceptual variations and/or measurement
errors at individual visits. In clinical practice, single-visit volume
measurements remain subject to potentially large errors that
should make physicians cautious before changing pump program-
mapping (or performing a device or component replacement proce-
dure) in the absence of drug underdose or overdose symptoms.
These measurements errors are particularly likely to occur in
the first few days or weeks after refill because of the small
volumes dispensed in that period. Individual measurement vari-
ability is illustrated by the approximately 4-fold difference in
the ordinate volume-ratio scale of Figure 3 versus Figure 2, as well
as the approximately 5-fold difference in the x-axis volume scales.

**FIGURE 3.** Per-refill accuracy ratios, from implant to 6 months after implantation (n=193 refills). Each refill visit’s data were used to calculate a ratio of observed volume dispensed to programmer-calculated amount dispensed. The individual ratios are plotted and summarized in
2 ways, including the circled outlier values (193 refills) and excluding them (189 refills).
A recent consensus paper reviews the subcutaneous tissue can result in a dangerous, possibly life-threatening, overdose. A return product analysis [pump lost in transit].

Physicians and practitioners should pay close attention to pump refill factors that may have influenced the measurements. Physicians returned product analysis [pump lost in transit].

Dwight syndrome in which the pump and catheter were replaced at 10.5 months (no returned product analysis revealed no anomaly); 1 drug withdrawal syndrome at 4.6 months (returned product analysis revealed no anomaly); 1 implant dislodgment, 2 catheter break/cut, 1 catheter disconnection at pump.

Any system-related event 38 (48), implant site effusion 11 (14), lumbar puncture headache 8 (10), catheter dislodgment 5 (6), implant site inflammation 4 (5), catheter break/cut 3 (4), implant site infection 3 (4), other AEs* 16 (20).

In Figure 3, several single, small (absolute) volume discrepancies apparently well outside the protocol specification (eg, ratio >1.25) were recorded, but turned out to be artifactual.

In terms of patient safety, a single discrepant refill needs to be considered within the context of patient symptoms and other factors that may have influenced the measurements. Physicians and practitioners should pay close attention to pump refill techniques because an inadvertent deposit of medication into the subcutaneous tissue can result in a dangerous, possibly life-threatening, overdose. A recent consensus paper reviews the pump’s safety issues.11 Clinicians are reminded that flow rate can vary from pump to pump, and the product labeling directs physicians to closely monitor patients following device implantation or replacement (eg, end-of-life pump replacement) and to titrate daily drug dosages gradually upward based on clinical effects, regardless of the individual’s intrathecal drug dosing history with their previous pump. A replacement pump that delivers a higher mean flow rate than the previous pump could compound problems associated with a patient becoming more or less drug-naive if there had been a lapse in therapy delivery related to the previous pump reaching its end of life. This highlights the importance of dosage titration after pump implant or replacement (eg, by direct weight) of minus 2.4% (SD, 2.1%) under controlled temperature and atmospheric pressure conditions. Laboratory investigation of the Synchromed II pump revealed a comparable flow-rate error (also by direct weight) of minus 2.4% (SD, 2.1%) under controlled temperature only. Direct fluid weight laboratory measures reduced measurement error especially at low flow rates.

The smaller flow-rate variations in laboratory data compared with clinical data in the present studies illustrate the limitations of clinical measurements and indicate that volume discrepancies from a single refill alone should not be relied upon as a decisive factor to assess pump performance or malfunctions.

The system-related AEs reported during the clinical study were similar in nature to those reported in the drug infusion therapy literature with predicate pumps.15–17 In the current clinical study, complications requiring surgical intervention on the infusion system were experienced by 14% of subjects, whereas the remainder of system-related AEs resolved following medical intervention. Ten percent of subjects experienced catheter complications. The manufacturer has subsequently introduced a new catheter designed to prevent common catheter complications and posts product performance reports annually at http://professional.medtronic.com/ppr/intrathecal-drug-delivery-systems/index.htm.

Clinical measurements of accuracy demonstrate real-world experience. These measurements are susceptible to sources of error unrelated to pump function. Bench data provide the pump’s actual accuracy, without the sources of error such as refill technique and imprecise measurement tools. Although individual pumps vary slightly in their average flow rates, the programmable pump allows the clinician to adjust flow rate (and thus the dose) according to the patient’s symptoms. The current study demonstrated that the Synchromed II pump accurately and safely delivered intrathecal medications in the clinical setting of this study.
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