

Mortality Associated with Implantation and Management of Intrathecal Opioid Drug Infusion Systems to Treat Noncancer Pain

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Background: **In 2006, the authors observed a cluster of three deaths, which circumstances suggested were opioid-related, within 1 day after placement of intrathecal opioid pumps for noncancer pain. Further investigation suggested that mortality among such patients was higher than previously appreciated. The authors performed investigations to quantify that mortality and compare the results to control populations, including spinal cord stimulation and low back surgery.**

Methods: **After analyzing nine index cases–three sentinel cases and six identified by a prospective strategy–the authors used epidemiological methods to investigate whether mortality rates reflected patient- or therapy-related differences. Mortality rates after intrathecal opioid therapy and spinal cord stimulation were derived by correlating Medtronic device registration data with deidentified data from the Social Security Death Master File. Aggregate demographic and comorbidity data were obtained from Medicare and United Healthcare population databases to examine the influence of demographics and comorbidities on mortality.**

Results: **Device registration and Social Security analyses revealed an intrathecal opioid therapy mortality rate of 0.088% at 3 days after implantation, 0.39% at 1 month, and 3.89% at 1 yr–a higher mortality than after spinal cord stimulation implants or after lumbar diskectomy in community hospitals. Demographic, illness profile, and mortality analyses of large databases suggest, despite limitations, that excess mortality was related to intrathecal opioid therapy, and could not be fully explained by other factors. These findings were consistent with the nine index cases that revealed that respiratory arrest caused or contributed to death in all patients. No device malfunctions associated with overinfusion were identified among cases where data were available.**

Conclusions: **Patients with noncancer pain treated with intrathecal opioid therapy experience increased mortality compared to similar patients treated by using other therapies. Respiratory depression as a consequence of intrathecal drug overdosage or mixed intrathecal and systemic drug interactions is one plausible, but hypothetical mechanism. The exact causes for patient deaths and the proportion of those deaths attributable to intrathecal opioid therapy remain to be determined. These findings, although based on incomplete information, suggest that it may be possible to reduce mortality in noncancer intrathecal opioid therapy patients.**

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INITIATION and management of intrathecal opioid therapy involve the transition from systemic to intrathecal drug dosing, and sometimes to intrathecal plus systemic dosing. Long-term intrathecal infusion of the approved formulation of preservative-free morphine sulfate (Infumorph® and Duramorph®; Baxter Healthcare, Deerfield, IL) by using implantable pump and catheter systems is a medically accepted, US Food and Drug Administration (FDA)–approved, and Medicare- or private insurance-reimbursed therapy for patients with otherwise chronic intractable cancer or noncancer pain. The current work focuses on intrathecal opioid therapy for chronic noncancer pain. Authoritative data regarding intrathecal opioid *versus* nonopioid intrathecal drug use are not available; however, information about intrathecal drug use in insurance databases and publications, including surveys of practitioners, reveals that exclusive use of nonopioid intrathecal analgesic drugs (*e.g.*, without an opioid drug admixture) is infrequent in the Unites States.[1–7] The intrathecal morphine sulfate label (package insert) contains drug dosage and patient care recommendations to help manage this therapy safely. The

Table 1. Information and Analyses for Each Data Source

Data Source	Description of Data
Index cases reported *via* MedWatch to the Food and Drug Administration	Identity, demographics, medical history, pain history, new or replacement device implant, intrathecal trial dose and technique, device implant history, operative and device programming data, intrathecal drug dose and concentration, systemic drugs at time of death, timeline of implant and facility discharge, timing and circumstances of death, autopsy and toxicological analyses, returned product device analysis.
Medtronic Enterprise Product Comment Report database	Number and dates of deaths among intrathecal opioid therapy pain patients voluntarily reported to Medtronic (Minneapolis, MN). Deaths after each type of pump event: new implant, pump replacement, catheter revision, pump refill, or reprogramming/dose change. Causality of reported deaths, when provided. Returned product analysis, when pumps or other device components are returned. Deaths by indication for pump use (nonmalignant pain, cancer, spasticity, other). Timing of deaths relative to pump event (within 3 days, not within 3 days, or unknown) and year of deaths. All deaths or serious injuries are reported periodically to the Food and Drug Administration; events that meet MedWatch criteria are reported expeditiously.
Device Registration System	Mortality rates–defined as deaths per 1,000 implants – within 3 days, 1 month, and 1 yr of implant with a Medtronic SynchroMed pump or spinal cord stimulation system between 1998 and 2006 by age, sex, and indication for implant. These were compared to expected mortality rates for the general US population based on tables from the National Center for Health Statistics.
Centers for Medicare and Medicaid Services*	Review of claims for a 5% sample of Medicare beneficiaries except those enrolled in health maintenance organization plans. Patients were included if they had claims for intrathecal opioid or spinal cord stimulator implants or no implant (control). Charlson comorbidity scores determined for 6-month baseline preimplant period. Percentage of patients who died within 1 year after implant and mean age at implant by study group (spinal cord stimulation, intrathecal opioid therapy, control, and pump implant survivors *vs* . decedents).
United Healthcare insured data*	Deidentified aggregate data on patients enrolled in the United Healthcare Insurance Plan who had a claim for intrathecal drug delivery or spinal cord stimulation, or intrathecal opioid trial without an implant (controls). Patients with cancer or spasticity diagnoses were excluded. Comparison groups (spinal cord stimulation, intrathecal opioid therapy, control) were matched for age and gender. Number and type of preindex (12 months before implant) healthcare visits, medical, and pharmacy data (prescriptions by therapeutic class); Charlson comorbidity score. Number of opioid prescriptions filled, in-hospital infections, discharge status of death, healthcare visits. Follow-up period defined as within 12 months after implant or index date for nonimplanted patients.
Published Case Series and Clinical Trials*	Demographics, medical and pain history, intrathecal and systemic drug use in intrathecal opioid, and spinal cord stimulation therapy patients. Nonmortality safety data in intrathecal opioid therapy series. Baseline demographics, medical history, and intrathecal and systemic drugs in ziconotide trials. Population-based mortality rates after lumbar diskectomy and other open spine surgery.

* See document, Supplemental Digital Content 1, which describes detailed methods and results, http://links.lww.com/ALN/A547.

results of a randomized controlled clinical trial that was monitored for drug-related toxicity as a safety endpoint support the use of intrathecal opioid therapy for cancer pain.[8] However, patients with noncancer pain presently comprise the majority of individuals implanted with intrathecal drug administration systems. Although the medical literature contains case series, review articles, consensus statements, and practice guidelines pertaining to this population, systematic safety, and efficacy data that meet a level of evidence comparable to that for cancer pain do not exist.[1–6]

Voluntary postmarket reports to Medtronic (Minneapolis, MN) of three patient deaths within 1 day after implant in February 2006 was the initial signal that postimplant mortality among intrathecal opioid patients with noncancer pain might be higher than previously appreciated. Regulatory affairs, postmarket vigilance, and medical advisory personnel formed an *ad hoc* team that identified a time-based cluster of early deaths by using a search strategy described in the Materials and Methods section. Medical review of the available data – including telephone interviews with implanting physicians and medical examiners–suggested that those deaths were attributable to overdoses of intrathecal opioids and/or systemic drugs. A preliminary statistical analysis found that early postimplant deaths were more frequent in noncancer pain patients treated with intrathecal opioids than in the first control samples that we identified–in particular, compared to patients treated with spinal cord stimulation. Only a small part of the mortality difference could be explained by age and sex

differences. Early in the investigation, we transmitted mortality case reports to the FDA as MedWatch reports. We also initiated contact with the agency to share the results of our initial analyses before formally communicating information to physicians in a Dear Doctor letter in 2006. One of the authors (Dr. Owens) led the epidemiologic analyses described in this article. Thereafter, we obtained deidentified data from United Healthcare and Medicare, and we analyzed data samples matched for age and sex to explore potential differences between intrathecal opioid and spinal cord stimulation therapy patients that might explain the differences in mortality. Those analyses could not explain increased mortality in the intrathecal opioid therapy population, especially within three days of implant. We then examined other procedures (intrathecal drug dose changes, pump programming and refills, and catheter interventions) that do not apply to spinal cord stimulation or other pain therapies – but that turned out to be temporally associated with mortality in intrathecal opioid therapy patients. Our analyses, as outlined here and detailed in the Materials and Methods, Results, and Discussion sections, suggest that a number of clinical factors likely caused or contributed to patient mortality; despite limitations in the data and our epidemiological approach, communication of these findings to physicians may help to reduce patient mortality.

Materials and Methods

We used an epidemiological approach to investigate mortality rates after intrathecal opioid drug delivery system implants in noncancer pain patients by using complementary data sources and statistical methods described herein. The principal objective that evolved during this project was to compare the observed rates of mortality at different intervals after intrathecal opioid drug delivery system implant or other delivery system-related events by using mortality rates in other populations as benchmarks–including mortality in patients who underwent open spine surgery or implantation of spinal cord stimulation systems. Depending on the particular source, different categories of data were collected and analyzed as summarized in table 1, which also reflects the temporal sequence of steps in the investigation.

No single database contained all of the information required to complete this project. We first focused on two internal data sources, the Enterprise Product Comment Report system (ePCR) and the Device Registration System (DRS), which are discussed in detail in the Index Cases and Product Comment Report System, and in the Device Registration System and Social Security Death Master File subsections. DRS data are matched on a monthly basis with the Social Security Administration (SS) Death Master File to provide a snapshot of patient survival after implantation of Medtronic devices. SS data are available to the medical device industry for purchase by subscription. However, ePCR, DRS, and SS data alone did not provide sufficient demographic or medical history information to compare mortality among matched patients treated by using different medical, surgical, or implant-based pain therapies–or *versus* other control populations. Consequently, we purchased more detailed data from the Centers for Medicare and Medicaid Services (CMS) and from United Healthcare (UHC). Those data permitted us to analyze control populations on the basis of demographics, medical comorbidities, drug prescriptions, and healthcare utilization.[9–11] Those data also permitted matched analyses of risk factors and mortality in cohorts with chronic pain treated medically, with an implanted intrathecal opioid drug delivery system, or with spinal cord stimulation–another implantable therapy for chronic pain. Summary results of the CMS and UHC data are discussed in this article, and detailed methods and results are presented in Supplemental Digital Content 1 (see document, which describes detailed methods and results, http://links.lww.com/ALN/A547), tables 1–4. We reviewed the published results of clinical trials, case series, consensus statements and surveys of intrathecal pain therapies,[12–21] spinal cord stimulation,[22–45] and population-based reports of mortality after conventional spine surgery.[46–49] The aim of those ancillary analyses was to clarify whether the mortality rates observed at different intervals after initiation of intrathecal opioid therapy were related to the therapy itself or the result of confounding factors such as age, gender, underlying medical conditions, or prescription drugs.

Index Cases and Product Comment Report System

The investigation began in the first 10 days of February 2006 when we received three voluntary reports from health professionals of mortality within 24 h after implantation of an intrathecal drug delivery system to treat noncancer pain. These are case numbers 1, 6, and 8 in table 2 and were recognized as a signal that further investigation was warranted. The next step was a prospectively defined and time-bounded search of the internal postmarket safety database (ePCR) for additional early postimplant death cases. The time boundaries were from December 1, 2005 (2 months before the first reports) to March 31, 2006 (almost 2 months after the first reports).

The ePCR system collects all spontaneous adverse event reports for Medtronic products, whether drug-related or device-related, from all sources. In a sense, ePCR is a complaint file, and all cases that involve mortality or other serious consequences as defined by FDA are reported through the MedWatch system. Categories of information collected through ePCR are summarized in table 1. Whenever possible, identifying patient data are collected in order to integrate data with the Device Registration System (de-

Table 2. Summary of Nine Index Cases of Death within 3 Days after Intrathecal Opioid Device Implant

Case Number	New or Replacement Device	Intrathecal Drug(s)	Drug/Dose (mg/d)/ Concentration (mg/ml)	Drug Analysis*	Pump Flow Rate (ml/d)	Pump Analysis†
1	New	HM–source unknown	HM/1.0/20	HM 14 mg/ml	0.05	Volume correct
2	New	MS–source unknown	MS/3.0/10	Not reported	0.3	Volume correct + no anomaly
3	New	Hospira MS	MS/4.0/20	MS 17.6 mg/ml	0.2	Volume correct
4	New	Infumorph MS	MS/0.99/10	Not reported	0.099	No data from ME
5	Pump replacement	Hospira MS	MS/1.2/25	MS 20.8 mg/ml	0.048	Volume correct
6	New	Compounded MS	MS/1.99/10	Not reported	0.199	Volume correct
7	Catheter replacement	HM + BUP–source unknown	HM/0.75/15, BUP/0.9/18	Not reported	0.466	Not explanted or tested
8	New	MS–source unknown	MS/0.75/10	Not reported	0.075	Not explanted or tested
9	New	Dilaudid HM +Lioresal	HM/2.1/6I, TB/0.175/0.5	Not reported	0.35	Not explanted or tested

scribed in the Device Registration System and Social Security Death Master File subsection). Limitations of voluntary reporting in ePCR include incomplete information captured for different cases, for example, on the cause of death, concomitant medications, or other medical data. ePCR reports are voluntary; therefore, the number of events in this database is an underestimate of what actually occurs. The reason to search for cases in the 4 months surrounding the three sentinel cases was to increase the likelihood of detecting a relationship between early mortality and potential drug or device manufacturing issues based on dates or lot numbers. We prespecified a 3-day postimplant window as the working definition for early mortality to account for delayed discovery or uncertainties regarding the time of death for unwitnessed cases. Table 2 summarizes the findings in nine cases between December 2005 and March 2006. These include the three sentinel cases (numbers 1, 6, and 8) plus six more cases (numbers 2, 3, 4, 5, 7, and 9) identified by the search strategy. Active investigation of these cases revealed more individual patient-, medical care-, drug-, and device-related data, and postmortem findings than are ordinarily captured through spontaneous, voluntary reporting activities to FDA.

Device Registration System and Social Security Death Master File

The Medtronic DRS also collects data mandated by FDA and the Code of Federal Regulations for implantable medical devices. Information captured by DRS is summarized in table 1, and it is patient-specific, identifiable, and in contrast to ePCR, prospectively collected. DRS data are available for greater than 90% of patients im-

Table 3. Unadjusted Death Rates for Benchmark Therapies: Lumbar Diskectomy, Lumbosacral Spine Surgery, Spinal Cord Stimulation Implantation,* and Intrathecal Drug Delivery Implantation for Noncancer Pain*

	Time After Implant		
	3 Days*	30 Days*	1 Year*
Noncancer pain intrathecal-opioid therapy 1998–2006	0.088%	0.39%	3.89%
Spinal cord stimulation therapy 1998–2006	0.011%	0.09%	1.36%
Unadjusted intrathecal opioid/spinal cord stimulation ratio	8.14	4.46	2.87
Age- and sex-standardized intrathecal opioid therapy/spinal cord stimulation rate ratio (95% CI)	7.56 (5.67–9.89)	3.64 (3.17–4.16)	2.25 (2.15–2.34)

	Time After Surgery		
	In-hospital	30 Days†	1 Year†
Community hospital diskectomy[44]	0.059%	Not reported	Not reported
Medicare lumbosacral spine surgery[45]	0.52%	0.31%	3.52%

Thirty-day and 1-yr mortality were not reported for the community hospital diskectomy series.

* Rates calculated from Medtronic Device Registration System and Social Security Administration Death Master File. Standardized rate ratios are based on the direct method of standardization; † for Medicare lumbosacral spine series, intervals are 30 days and 1-yr posthospital discharge.

Table 2. Continued

Programmed Morphine-equivalent Dose (mg/d)‡	Other Opioids or Central Nervous System Depressants Prescribed	Opioid-related Risk Factors	Time/Location of Death	Cause of Death§	Prodromal Symptoms of Overdose‖
3.0–6.0	Yes	No	<1 d/home	O.D.	Yes
3.0	Yes	No	1 d/home (car)	O.D.	Yes
4.0	Yes	No	<1 d/home	O.D.	Yes
0.99	Yes	Obesity, short neck	<1 d/home	O.D.	Yes
1.2	Yes	No	<1 d/home	O.D.	Not reported
1.99	Yes	No	<2 d/home	O.D.	Not reported
2.25–4.5	Not reported	Age 79 yrs, COPD, asbestosis	<1 d/emergency room	Aspiration, O.D.	Not reported
0.75	Yes	Obesity	<1 d/home	O.D.	Yes
6.3–12.6	Yes	Age 79 yrs cancer	<6 h/inpatient	Probable O.D.	Yes

Case 5, catheter was found disconnected 1 week before a new system implant and had been disconnected for an indeterminate period; case 7, catheter was dislodged for an indeterminate period of weeks to months before catheter revision.

* Analysis of pump reservoir contents reveals that the doses administered to case 1 = 0.7 mg/d HM; case 3 = 3.52 mg/d MS; case 5 = 0.99 mg/d MS; † postmortem analysis of pump residual volume and/or functionality; ‡ MS-equivalent dose = mg/d hydromorphone × conversion factor (published range = 3:1–6:1); § cause of death based on all available information; ‖ prodromal symptoms: lethargy, drowsiness, somnolence, respiratory depression, apneic periods, and/or snoring.

BUP = bupivacaine; COPD = chronic obstructive pulmonary disease; HM = hydromorphone; ITB = intrathecal baclofen; ME = medical examiner; MS = morphine sulfate; O.D.= opioid and respiratory depressant drug overdose.

planted in the United States to treat chronic noncancer pain with Medtronic intrathecal opioid delivery or spinal cord stimulation systems. Matching of DRS data and the SS Death Master File—a database that gathers information reported to state vital records offices—allowed us to compare mortality rates at selected intervals after implantation with either an intrathecal opioid drug delivery or spinal cord stimulation device. In 2006, we prospectively established the time window to investigate postimplant mortality with either device as any implant that occurred between May 1998 and December 2004 to allow 1-yr follow-up through January 1, 2006. Time intervals chosen for analysis were in the first 3 days, in the first 30 days, and in the first year after implant. Age and gender-adjusted comparisons of death rates for patients with intrathecal opioid delivery and spinal cord stimulation systems employed direct standardization to the combined populations of all patients with either device. We assumed for the purpose of this analysis that devices remained in use for at least 1 yr (no censoring) because of the limitation that DRS does not always record whether or when devices in living patients are explanted or allowed to remain unused. An additional limitation is that DRS records include the indication for intrathecal opioid therapy (*e.g.*, noncancer pain) but not the intrathecal or systemic medications being used. However, data about intrathecal drugs and concomitant medications were available for analyses of the other data sources listed in table 1 and discussed in the Results section.

Table 4. Deaths/Expected Deaths Ratios for Intrathecal Opioid and Spinal Cord Stimulation Patients by Time Period

	Mortality within Time Period		
	3 Days	30 Days	1 Year
Intrathecal opioid deaths/expected deaths* (95% CI)	7.5 (5.7–9.8)	3.4 (2.9–3.8)	2.7 (2.6–2.8)
Spinal cord stimulation deaths/expected deaths* (95% CI)	1.4 (0.6–2.6)	1.1 (0.9–1.4)	1.4 (1.3–1.5)

* Intrathecal therapy and spinal cord stimulation death rates calculated from Medtronic Device Registration System and Social Security Administration Death Master File. Expected deaths based on age and gender-specific US period life table (2002). Table values are mortality ratios standardized to the age- and sex-matched US population and 95% confidence limits.

Patients implanted with spinal cord stimulation devices served as one of the benchmark control groups for this and other analyses because, despite certain differences, patients treated by using intrathecal opioid or spinal cord stimulation therapies most commonly suffer from chronic noncancer pain that does not respond adequately to other therapies, including systemic opioid drugs. The surgical implant procedures for drug delivery and spinal cord stimulation are similar to each other, and neither involves surgical entry into a body cavity. Moreover, mortality data for the two devices in DRS are expected to be equally complete. For the cohorts with each device, the expected numbers of deaths over the 3-day, 30-day, or 1-yr time intervals were calculated on the basis of published actuarial tables for the overall US population by age and gender. The ratio of observed to expected deaths is the standardized mortality ratio, and confidence limits for these ratios were calculated by using Byar's method.[50] The age and gender distributions of the populations with intrathecal opioid delivery and spinal cord stimulation systems are different; for comparison of the mortality experience of these two populations, the method of direct standardization was used, with weights calculated from the overall distribution of subjects with either device.

Additional Analyses–Product Comment Report System

Examination of the nine index cases and the comparison of mortality rates between intrathecal opioid patients and spinal cord stimulation patients suggested possible explanations for 3-day postimplant mortality. Preliminary analyses of 30-day and 1-yr mortality also suggested a longer-term excess in mortality among intrathecal opioid patients compared to spinal cord stimulation and other populations. Consequently, we performed additional analyses on 1,851 ePCR reports for intrathecal opioid therapy implants and mortality that occurred during the same interval as the DRS analysis (described in the preceding two paragraphs). The additional analyses of ePCR complaint files evaluated deaths reported to have occurred within 3 days of a new intrathecal opioid therapy system implant and expanded to include deaths that occurred within 3 days after any pump refill, pump replacement, catheter revision, pump programming session, or drug dose change. A limitation of this additional analysis is that the date of death–with respect to device implants, replacements, revisions, refills, or programming–was reported for only 36% of noncancer pain cases (201 of 557). Within limitations imposed by the reported data, the analysis revealed temporal relationships between patient deaths and the listed interventions.

Results

Index Cases

The clinical features of the nine cases identified between December 2005 and March 2006 and the medical circumstances surrounding their deaths are summarized in table 2. Analysis of clinical, postmortem, and toxicological data indicate that the cause of death involved opioid and/or central nervous system depressant drug overdose as a primary or contributing factor in every case. Eight of the nine patients had noncancer pain, and one patient had cancer pain. Eight of the nine patients, seven with noncancer pain plus the one with cancer pain, died within 24 h after a new device implant, pump replacement, or catheter revision. One of the nine patients died within 48 h after hospital discharge. Seven cases underwent new intrathecal opioid delivery system implants, and two had intrathecal opioid delivery restored weeks or longer after catheter dislodgement or temporary pump removal–the latter performed for a mistaken diagnosis of pump pocket infection. Seven cases (numbers 1, 2, 3, 5, 6, 7, and 9) were programmed to receive an intrathecal morphine or morphine-equivalent dosage of hydromorphone that exceeded the starting dose for intrathecal opioid naïve patients recommended in the Infumorph labeling (recommended starting dose = 0.2–1.0 mg/d for individuals without opioid tolerance). The other two cases (numbers 4 and 8) were programmed to receive less than 1.0 mg/d intrathecal morphine (0.99 and 0.75 mg/d, respectively), but they died from respiratory arrest resulting from apparent intrathecal opioid or mixed intrathecal opioid plus concomitant systemic drug overdose after hospital or surgical center discharge. Errors in dosage calculations or pump programming caused or contributed to two deaths (cases 7 and 9). Case 9 died within hours after a new system implant and initiation of therapy with hydromorphone and baclofen.

Apart from the medical causes and circumstances of death for these nine cases, we also performed analyses to determine whether this cluster of events was associated with time-, drug-, or device-related factors. Data were segmented according to the date of surgery or death, by date of device manufacture, and by device serial or lot number. None of the device analyses revealed a clear signal or trend, and the intrathecal drugs administered were from multiple manufacturers or pharmacies. Thus, the nine cases from December 2005 to March 2006 did not constitute an outbreak or epidemic that could be traced to a particular source or cause. Rather, the cases constituted a coincidental temporal cluster within the large data set of intrathecal opioid therapy implants for noncancer pain.

Device Registration System and Social Security Death Master File

The mortality rates calculated from DRS and SS data within 3 days, 30 days, and 1 yr after intrathecal opioid delivery system implant are summarized in table 3. Corresponding DRS/SS data for mortality after implant of a spinal cord stimulation system are also shown. For benchmarking purposes, published in-hospital mortality rates after lumbar diskectomy in a nationwide community hospital sample[43,44] and mortality after a variety of lumbosacral spine operations in Medicare beneficiaries[45] are also provided. In-hospital mortality after lumbar spine surgery varied with the population under study and the complexity of the operations performed. The lowest mortality rate, 0.059% (0.59 per 1,000 procedures) occurred among diskectomy patients in the community hospital setting. Hospital mortality among older Medicare beneficiaries who underwent more complex operations, such as multilevel surgery and/or fusion, was an order of magnitude higher: 0.52% (5.2 per 1,000 procedures). Thirty-day and 1-yr mortality in the Medicare population also are presented in table 3.

Mortality within 3 days after intrathecal opioid system implantation was 0.088% (0.88 per 1,000)– higher than the community hospital diskectomy population (0.59 per 1,000) but lower than the Medicare spine surgery population (5.2 per 1,000). The 0.088% 3-day intrathecal opioid mortality rate also was eight times greater than the 0.011% (0.11 per 1,000) 3-day mortality rate after spinal cord stimulator implantation. The mortality rate in the intrathecal opioid population remained higher, albeit by lower proportions, than in the spinal cord stimulation

population at 30 days and 1 yr after implant. Standardization to the overall age and sex distribution of the population implanted with either system makes the intrathecal opioid therapy and spinal cord stimulation rates directly comparable without confounding by age and sex differences (*e.g.*, average age higher by 4.6 yr at implant for intrathecal opioid compared to spinal cord stimulation patients). This suggests that the observed excess mortality was attributable to intrathecal opioid therapy and not to age or gender differences. The fourth row of table 3 shows the standardized mortality ratios for intrathecal opioid/spinal cord stimulation patients. Those ratios are only slightly smaller than the unadjusted (for age and sex) ratios of rates in the third row of table 3, again indicating that age and gender differences accounted for only a small portion of the difference in mortality observed in this population for the two therapies. Confidence intervals for these ratios exclude unity, indicating that the excess mortality among intrathecal opioid patients is highly statistically significant.

Table 4 shows the ratios of the number of deaths in the intrathecal-opioid cohort and spinal cord stimulation cohort to the number of deaths that would have been expected on the basis of the overall age- and gender-specific mortality rates for the US population in 2002 (a ratio of 1.0 would indicate no excess mortality). The ratios of observed deaths for noncancer intrathecal opioid therapy patients to the number of expected deaths (7.5:1 at 3 days, 3.4:1 at 30 days, and 2.7:1 at 1 yr) remained higher at all intervals compared to spinal cord stimulation patients (1.4:1, 1.1:1, and 1.4:1, respectively). Confidence limits for the spinal cord stimulation ratios are close to or include unity, indicating that mortality was not greater than expected for spinal cord stimulation patients.

Product Comment Report Database and Returned Product Analysis

Evaluation of 557 ePCR reports of noncancer pain intrathecal opioid therapy patient deaths between 1998 and 2007 revealed that 88 cases (15.8%) were reported to have occurred within 3 days of a pump implant, refill, replacement, reprogramming, dose change, or catheter revision (table 5). Another 113 deaths occurred more than 3 days after any of those procedures for a total of 201 cases (36% of 557) with a known time of death. A reported cause of death was available for 55 (62.5%) of the 88 death cases within 3 days of an implant, refill, replacement, reprogramming, dose change, or catheter revision as summarized in table 6. Suspected or confirmed drug overdose was the most frequently reported cause reported by physicians (25/55 cases). When data are tabulated by the type of device-related procedure (table 7), deaths within 3 days of an initial implant or pump replacement account for half of the observed mortality, despite the infrequency of these procedures relative to the number of refills and dose changes. These data include spontaneously reported deaths, only—in contrast to the more comprehensive DRS-SS analysis described in the preceding paragraph. One should interpret the ePCR data cautiously because of that limitation.

Pumps were returned for analysis in 41 ePCR mortality cases. Analysis revealed an abnormality in 8 (19.5%) of 41 cases. Deidentified raw data for those eight cases are provided in table 5, Supplemental Digital Content 1 (see document, which is a table summarizing device analysis results, http://links.lww.com/ALN/A547). Abnormal findings included battery depletion/end of life (n = 2), pump memory errors (n = 2), reservoir septum damage (n = 2), broken motor screws (n = 1), and bridging residue on

Table 5. Time of Death in Noncancer Pain Patients in Relation to a Pump Implant, Refill, Replacement, Programming, Dose Change, or Catheter Revision–From Enterprise Product Comment Report System

Time of Death	Number of Patients (%)
Within 3 days	88 (16%)
After 3 days	113 (20%)
Unknown	356 (64%)
Total	557 (100%)

Table 6. Reported Cause of Death in Noncancer Pain Patients within 3 Days of a Pump Implant, Refill, Replacement, Programming, Dose Change, or Catheter Revision–From Enterprise Product Comment Report System*

Reported Cause of Death	Number of Patients (%)
Drug overdose (confirmed or suspected)	25 (28.4%)
Cardiac event, infarct, or coronary disease	14 (15.8%)
Pulmonary embolus	3 (3.4%)
Drug refill through catheter access port	2 (2.2%)
Respiratory arrest	2 (2.2%)
Stroke or brain hemorrhage	2 (2.2%)
Sudden death–not otherwise specified	1 (1.1%)
Suicide	1 (1.1%)
Multiorgan failure	1 (1.1%)
Natural causes	1 (1.1%)
Complications of epilepsy	1 (1.1%)
Sleep apnea	1 (1.1%)
Aspiration pneumonia	1 (1.1%)
Not reported	33 (37.5%)
Total	88 (100%)

* One patient died within 3 days of both pump refill and replacement.

Table 7. Noncancer Pain Patient Deaths within 3 Days by Pump- or Device-related Procedure–From Enterprise Product Comment Report System

Device-related Procedure	Noncancer Deaths within 3 Days, n (%)
Implant	30 (34.0%)
Pump refill	28 (32%)
Pump replacement	14 (16%)
Catheter revision	12 (13.5%)
Reprogramming/ dose change	4 (4.5%)
Total	88 (100%)

gears (n = 1). Battery depletion/end of life means that the pump is stopped and no longer dispensing fluid. Pump memory error is a programmer display that happens when the most recent (or current) programming session is unsuccessful because of background interference, most commonly if the device and programmer are too close to a television or computer screen, or if programming is attempted postmortem or after explant when the pump (or body) is at room temperature. A memory error does not indicate pump damage, but the pump may stop or revert to the previously programmed settings. Reservoir septum damage is a visual observation of the refill port septum, which indicates only that the pump has been refilled many times, but has no influence on pump function. Broken motor screws and bridging residue on gears are caused by use of specific off-label drugs—for example, meperidine (United States), diacetyl morphine (United Kingdom)—that are chemically incompatible with pump components, and eventually leak into the pump mechanism.[6] These ultimately cause the pump to stall, with the stalled condition displayed on the programmer screen during the next physician visit. However, the two affected pumps described here had not yet stalled. Abnormal observations in these eight devices could not directly cause patient mortality from intrathecal drug overdose because the findings either had no influence on flow rate accuracy, or caused the affected pumps to cease infusion rather than to overinfuse the intrathecal drugs.

The 33 returned pumps (80.5%) that showed no anomalies included all of the pumps in the ePCR database that were explanted postmortem from individuals who died within a few hours or days after implantation. Returned product analysis and/or interrogation and aspiration of pump contents by medical examiners in five of the nine index cases also revealed that the expected *versus* actual residual volume of drug in the pump reservoir was within device accuracy specifications. In three of the index cases, pump performance data were unavailable because the device was not removed before burial, and in one additional case because the medical examiner would not disclose information.

Discussion

Limitations of the Analyses

The data, analyses, and conclusions of this investigation are subject to several limitations. As described in the Methods section, active investigation of the nine index cases provided detailed data that are not ordinarily captured by passive processes for spontaneously reported adverse events. Therefore, in contrast to the nine index cases, analyses conducted on the larger set of ePCR data reported by healthcare professionals or family members between 2005 and 2007 were intentionally limited to date of death, reported cause of death, and temporal relationship to a pump implant or replacement or to other procedure as described in the Results section and tables 5 and 6. Those analyses were further limited by gaps in the spontaneously reported data. A time of death was not reported in 64% of ePCR death cases (356 of 557), and a cause of death was not reported in 37.5% of mortality cases (33 of 88) that occurred within 3 days of a pump or system procedure.

Investigation of the nine index cases (table 2) also left gaps in the data, especially regarding the sources of intrathecal drugs and postmortem analysis of the pump reservoir contents. Among the six cases receiving intrathecal morphine (all as monotherapy), two were administered a parenteral morphine formulation not labeled for intrathecal use (Hospira Healthcare, Inc., Lake Forest, IL), two were administered morphine for which the drug source (commercial or compounded) could not be determined, and one case each was administered hospital-compounded morphine sulfate or the approved formulation of Infumorph. Among the three cases treated by using hydromorphone (monotherapy in one case, admixture in two cases), one received Dilaudid (Knoll Pharmaceutical Co., Mt. Olive, NJ), and the drug source could not be determined in two cases. In three cases, the concentration of hydromorphone (case 1, unknown source) or morphine (cases 3 and 5, Hospira) were measured postmortem and found to be lower than what the implanting physicians had programmed into the pump. It is possible, albeit speculative, that pharmacists made drug compounding or dilution errors in these individual cases. Another explanation for lower than expected reservoir concentrations is that implanters were unable to completely aspirate all of the sterile water that remains in the pump reservoir after manufacturing. This manufacturing step ensures that pumps can be factory-set to run at a minimal shelf state and not stall during prolonged shelf life. It is also possible that both mechanisms contributed to the lower observed drug concentrations in these cases. Table 2 notes that two of the index cases (cases 4 and 8) were obese. We could not examine whether body habitus or obesity contributed to postanesthetic or delayed patient deaths in other populations because body weight or body mass index values were not included in the data sets.

Device stoppage or underinfusion was unlikely to have been followed by uncontrolled pain and fatally excessive oral medication intake among the nine index cases or in seven of eight of the 3-day postimplant cases identified in the 2005–2007 ePCR analysis. The patients in both data sets died before experiencing intrathecal drug-mediated analgesic effects for a long enough period to have experienced pain recurrence before death. However, it is theoretically possible that case 3 (battery end of life) in table 5, Supplemental Digital Content 1 (see document, a table summarizing device analysis results, http://links.lww.com/ALN/A547) or other patients who died after months or years on intrathecal opioid

therapy—and who had stopped or underinfusing pumps identified at the time of death—could have unintentionally overdosed themselves on systemic medications because of recurrent pain. Among the 19.5% of pumps (8 of 41 returns in 557 deaths in ePCR) that had anomalies detected by returned product analysis, two pumps had dead batteries and definitely were nonfunctioning, and another two were in a "pump memory error" state that can cause pump stoppage with clinical consequences if stoppage occurs before death. However, a pump memory error also can occur if a pump is interrogated during postmortem investigations or after being returned to a physician after explant by mortuary personnel. The available data do not reveal when those pumps entered the memory error state—in life or after explant (table 5, Supplemental Digital Content 1, which summarizes device analysis results, http://links.lww.com/ALN/A547).

The Device Registration System captures individual patient identification data, including age and sex, implanting physician and insitution data, the serial and/or lot number(s) of the implanted device(s), the date of implant, and the patient's underlying diagnosis or indication for device implantation. DRS does not collect any other medical or health-related information. The SS Death Master File provides the identity and date of death of deceased individuals, but it does not report the cause of death or other medical information. The DRS and SS data correlation that we performed for patients with noncancer pain implanted with intrathecal opioid delivery or spinal cord stimulation systems demonstrated a clear excess in early deaths among intrathecal opioid patients that could not be explained by differences in age and gender, but the data could not rule out other potential differences between these cohorts that might be explanatory. Our DRS data do not include any information on medical history or other factors that could potentially explain the differences in mortality for these two cohorts; we therefore purchased data from the CMS and UHC to specifically analyze whether differences in underlying medical comorbidities, physician-prescribed drugs, healthcare utilization, as well as age and sex, could explain any of the observed mortality difference between noncancer pain patients treated by using intrathecal opioid and spinal cord stimulation therapy (methods described in detail in Supplemental Digital Content 1 [see document, http://links.lww.com/ALN/A547]). Therapy-specific data from CMS and UHC (intrathecal opioids, spinal cord stimulation, or no invasive therapy) permitted similar analyses as the DRS-SS data but included devices made by all manufacturers and with the ability to control for demographic and medical comorbidities.

Mortality was the endpoint that we investigated on the basis of an initial safety signal and a temporal cluster of events. Nonfatal procedure- or therapy-related injuries that lead to disability or potential loss of life years afterwards are other important topics that deserve examination in the future. A discussion of other limitations and mitigating factors pertaining to analyses of the CMS and UHC data sets also appears in Supplemental Digital Content 1 (see document, http://links.lww.com/ALN/A547).

Interpretation and Implications of the Results

Analyses of data from multiple complementary internal and population-based sources indicate that noncancer pain patients treated with intrathecal opioid therapy experience elevated 3-day, 30-day, and 1-yr mortality compared to patients treated by using spinal cord stimulation, another device-based therapy that involves a similar, albeit not identical, implant procedure. Intrathecal opioid therapy patients also experience slightly higher 3-day mortality compared to in-hospital deaths for community hospital lumbar diskectomy patients, and intrathecal opioid patients experience higher 30-day and 1-yr mortality (but lower 3-day or in-hospital mortality) than Medicare patients who undergo more complex spinal operations. Although a larger proportion of intrathecal opioid implant procedures compared to spinal cord stimulation procedures are performed under general anesthesia, none of the demographic, concomitant illness, or other healthcare utilization data that we reviewed suggest that increased anesthetic risks were responsible for the mortality differences that we observed. Absolute and comparative mortality rates for intrathecal opioid therapy initiation and maintenance had not been identified or explored systematically before this investigation. One possible reason for underappreciation of the risks that we identified include the low likelihood that an individual physician would observe early postimplant mortality, which occurs at a rate of fewer than one per 1,000 device implant or component replacement procedures.

This investigation began when three sentinel reports in February 2006 and six subsequently identified nearly contemporaneous cases (nine index cases) suggested that intrathecal opioids, or mixed intrathecal opioid plus systemic drug interactions, caused fatal respiratory depression. Available data from the index cases, and from a follow-on investigation in the ePCR data base, albeit subject to limitations described in the opening paragraphs of this Discussion section, revealed that in cases where pump volumes or performance were checked postmortem, device-related malfunctions or overinfusion did not cause intrathecal overdosage and death. One important limitation of this finding that bears repeating is that fewer than 10% of death cases in the ePCR database were accompanied by returned products for analysis. Therefore, one cannot infer that device malfunctions or overinfusion events were absent in the 90% of deaths where residual volumes were not analyzed or devices were not returned. The major finding from the index cases is that early deaths do occur as an apparent result of intrathecal and systemic opioid overdose and

that all spontaneously-reported early deaths in the 4-month analysis window were variations on this theme.

The DRS-SS analysis revealed that the excess mortality risk of intrathecal opioid mortality *versus* spinal cord stimulation was 7.56:1 at 3 days, 3.64:1 at 30 days, and 2.25:1 at 1-yr postimplant, after adjustment for age and gender. Although the relative risk is greatest shortly after implant, the largest number of deaths occurs during therapy maintenance. Analysis of spontaneously reported ePCR data beyond the index cases, despite the limitations that we have enumerated, suggested a temporal relationship between mortality and pump refill or programming procedures (in addition to implant or replacement procedures). That analysis suggests, but does not prove, that elevated 30-day and 1-yr mortality among intrathecal opioid therapy patients may also be therapy-related.

Large population-based analyses point in the same direction as the internal data; intrathecal opioid therapy patients experience excess mortality risks *versus* control- or matched control populations treated differently. Those same sources, especially the UHC cohorts, also did not support the anecdotal notion that intrathecal opioid patients, when matched for age and gender, are sicker, are at higher risk for nontherapy-related death, or have more drugs prescribed than spinal cord stimulation or nonimplanted patients. Intrathecal opioid patients also must undergo pump refills, each of which carries additional risks, as identified by the persistently elevated 30-day and 1-yr mortality compared to spinal cord stimulation patients, who only experience additional device risks if they undergo a revision or replacement procedure.

The finding that most of the mortality occurred out of hospital in each data set that we analyzed dovetails with recent publications and news reports that described unexpectedly high outpatient mortality rates associated with systemic opioid prescriptions accompanied by other medication and respiratory depressant substance intake, including alcohol and prescribed or illicit drugs.[51–53] Removing the stigma for pain patients and lowering the barriers for physicians to prescribe chronic opioid analgesics undoubtedly has reduced pain and suffering. Those benefits are accompanied by risks. In a recent population-based study of mortality after lumbar spine fusion surgery, analgesic-related deaths were the single largest cause of mortality, accounting for 21% of deaths and 31.4% of potential life lost.[46] Still, one cannot infer that because nine index cases died from apparent intrathecal opioid or intrathecal opioid plus systemic drug-induced respiratory depression that the other intrathecal therapy death cases in databases that we examined (DRS, ePCR, CMS, or UHC) also must have died from drug-induced respiratory depression. Rather, all of the analyses identified excess mortality among intrathecal opioid patients, that excess mortality was at least partly therapy-related, and that a candidate for further investigation is intrathecal or intrathecal plus systemic drug-induced respiratory depression. Even a cautious interpretation of these results raises the question of what physicians and industry can do now, albeit based on incomplete and imperfect information, to reduce the preventable proportion of mortality associated with intrathecal opioid therapy for noncancer pain. Physicians may wish to critically examine the prescribing information, precautions (including special populations), and warnings contained in the Infumorph and Duramorph labeling. Concerns about potentially fatal respiratory depression after even small doses of intrathecal morphine have a sound physiologic and experimentally demonstrable basis.[54,55]

Morphine sulfate labeling and safety information should apply to hydromorphone (from 3:1 to 6:1 higher potency than morphine, depending on the reference[56]) and other opioids, even though the latter are not FDA-approved for chronic intrathecal administration. With respect to device-related aspects of therapy, two patient deaths among the nine index cases were caused by pump programming and/or intrathecal dose calculation errors. This suggests that improvements in physician education and in the device interface–including greater simplicity, and improved device-generated alerts–also are important changes to enhance patient safety.

Conclusions

Despite limitations of the data and analyses for each component of this investigation, the finding of excess early and delayed mortality associated with intrathecal opioid therapy for noncancer pain appears genuine. Physicians and industry are now confronted with the challenge and opportunity to reduce the preventable portion of the excess mortality described in this article. Further investigations, educational efforts, and– ultimately– changes in medical practices may be required.

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