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Death after Initiation of Intrathecal Drug Therapy for Chronic Pain

Assessing Risk and Designing Prevention

THE use of intrathecal drug delivery has emerged as a viable option for the long-term treatment of cancer-related pain, and significant evidence has emerged to bolster its place in our pain treatment armamentarium.[1,2] Use of this therapy has grown dramatically for chronic noncancer pain, particularly for the treatment of chronic back pain.[2] The evidence to support efficacy in this realm is growing, but it remains inadequate; patient selection remains empiric, and efficacy and long-term safety have yet to be established.[3] At the same time, the complications associated with this long-term therapy have grown more evident, particularly the appearance of neurologic injury associated with catheter-tip granuloma formation.[4] It is now clear that many of the actual drug combinations and concentrations in clinical use had not been adequately tested in preclinical models.[5] In this issue of ANESTHESIOLOGY, the manufacturer of the most common device used to provide intrathecal therapy details a series of deaths reported within 1 day of implant in February 2006.[6] The manufacturer has teamed with a group of experts and has used large databases to understand if this therapy is indeed associated with excess mortality. They conclude that patients with noncancer pain treated with intrathecal opioid therapy experience increased mortality compared to similar patients treated by using other therapies. This is a striking conclusion, and many questions arise. Is this excess mortality real or an artifact of the methodology used? What can we learn from the analysis to improve the safety of intrathecal drug therapy? Are there improvements in the technology associated with this device that could be applied to improve its safety?

Is this excess mortality real or an artifact of an imperfect analysis? One of the strengths of the study data set is that the large, stable study population affords a look at a variety of concomitant medications and important subgroups. Adequate sample size allowed the authors to restrict their exposure groups to new initiators of the opioid delivery devices and to control for several potential confounders using what amounts to an incident user cohort design. An incident user design reduces the likelihood of missing early adverse events, allows for an evaluation of risks over time, ensures that the assessment of patient baseline characteristics is uninfluenced by any effects of exposure/treatment, and reduces the likelihood that treatment assignment is influenced by past experience. To have unadulterated exposure groups, the authors compared monotherapies with each other and censored patient follow-up as soon as the patient switched devices or augmented therapy with other devices. This analytic strategy makes treatment groups comparable with regard to initial health state and avoids comparing patients who change treatment groups in response to treatment failure or side effects to those who do not. In addition, automated pharmacy records are a good source of medication data because these records are not subject to information bias. Residual misclassification is conservative, mitigating against bias that would favor detecting a drug effect.

Despite the strengths in the study design, the study may resist generality beyond patients receiving intrathecal opioid *versus* spinal cord stimulation as monotherapy, a limitation that affects generality to a large proportion of patients because many patients who receive treatment with spinal cord stimulation are also receiving a range of other treatments concomitantly. The current study has limited ability to adjust for confounders such as severity of illness and circumstances surrounding the events (deaths). The authors attend to these critical issues by conducting several sensitivity analyses with other data sets, and they make a compelling argument for consistency of gross effects, but results may not be applicable to other groups of patients, *e.g.*, younger ones. The authors might have considered sensitivity analyses that examine residual confounding using propensity score calibration and instrumental variable techniques, which allow more efficient matching than standard regression procedures when examining a rare outcome.

So, the conclusion that initiation of treatment with intrathecal opioid therapy results in excess mortality appears to be sound. Where might these risks arise, and how can we alter our practice to minimize risk? Unfortunately, the large database analyses do not answer these questions, and we must turn to clinical experience and the scant information that can be gleaned from the index cases in the current report. The use of intrathecal drug therapy is technically challenging and relies on an understanding of the pharmacology of intrathecal opioids and proper use of the infusion device. The role of the individual practitioner is critical in assuring safe initia-

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tion of intrathecal opioid therapy. We know that the pharmacodynamic effects of intrathecal opioids are very different than those of the same agents administered intravenously or orally.[7]

Intrathecal administration of morphine is associated with a small incidence of delayed respiratory depression that can appear as long as 18–24 h after the initiation of therapy.[8,9] Added to this is the marked uncertainty when converting large systemic doses of opioid to equivalent intrathecal doses.[10]

Practitioner error can also enter during the initial programming of the intrathecal drug delivery device. The drug concentration must be entered manually, and the dead space volume between the implanted drug reservoir and the tip of the intrathecal catheter must also be entered manually at the time of implantation.

Practitioners often use concentrated opioid solutions to maximize the interval between refills of the drug reservoir. Look at the Medtronic SynchroMed® II (Medtronic, Minneapolis, MN) pump‡ as an example (the most common pump currently in use world wide). This pump has a drug reservoir that holds 20 ml. The volume between the drug reservoir and the catheter tip depends on the amount of the catheter that is trimmed off at the time of implantation, but it is typically about 0.4 ml. The pump is capable of delivering 0.048 ml or more of solution accurately over each 24-h interval. If a patient is receiving 1 mg/d morphine using a solution that contains 10 mg/ml, it will require 4 days for the drug solution to reach the catheter tip. Thus, the onset of drug effect can begin many days after the implantation, at a time when both patient and practitioner vigilance regarding the effects from the surgery is likely to be low.

Even more problematic is the difficulty in safely programming the pump to deliver a bolus of medication aimed at clearing the catheter of previous drug and introducing a new drug and/or a new drug concentration. Although the pump's programming device has the capability to simplify the dosing, there are no safeguards that alert the practitioner when a potentially lethal overdose has been programmed into the device.

How much of the excess mortality identified is practitioner error? It is impossible to determine from the present analysis, but a detailed look at the nine fatalities reveals some common themes. Drug overdose was the likely cause of death in all nine cases. Seven of the nine fatalities occurred after placement of new devices, all occurred within 2 days after implantation, and eight of nine occurred after discharge from the hospital. Concentrated drug solutions and low infusion rates were common, and all patients were receiving opioid in the intrathecal solution. The majority of patients had been prescribed concomitant oral opioids or other central nervous system depressants.

Would additional monitoring have prevented some or all of these deaths? It is impossible to be certain. It is clear from our experience with intrathecal opioid analgesia that monitoring of respiratory status on a typical postoperative ward is not always sufficient to prevent clinically meaningful respiratory depression.[11]

How then should we proceed? Every practitioner using intrathecal therapy must understand that there is risk of fatality, particularly soon after implantation. In the absence of data to guide practice, we must adopt a common sense approach. It seems logical that practitioners can minimize their contribution to this risk by (1) initiating intrathecal therapy with the lowest dose that can be reasonably predicted to provide efficacy; (2) avoiding use of concomitant central nervous system depressants in the immediate postimplantation period; (3) gaining an expert understanding of the intrathecal drug pump, its construction, and proper programming; (4) personally overseeing all aspects of the initial programming; (5) avoiding use of excessively concentrated solutions during initiation of therapy to minimize the delay in onset of drug effects associated with slow infusion rates; and (6) routinely calculating when new drug will first enter the intrathecal space and warning the patient and their caregivers to be most vigilant during this interval of time.

Can technology be an aide? Through provision of education, device manufacturers can help to assure that each practitioner that uses intrathecal drug delivery is fully versed in the safest use of the technology. More importantly, device and drug manufacturers can work with expert practitioners to devise guidelines for initiation of therapy, which include recommended maximum initial drug concentrations. Limits to prevent a practitioner from unknowingly exceeding these maximum initial doses can be programmed directly in to the device, with a warning to the practitioner if they are attempting to program delivery of a potentially life-threatening dose of a drug. Indeed, such a dose-limiting approach has been proposed as a top priority to improve the safety of intravenous infusion systems.[12] Finally, simplifying the programming of the device, particularly the programming necessary to deliver a bolus dose when the dose or concentration in the reservoir is being increased may well improve safety. For now, practitioners should remain vigilant to the added potential risk of fatal drug overdose whenever intrathecal opioid therapy is first initiated or immediately after a drug delivery system is replaced.

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‡ Technical information available at http://professional.medtronic.com/devices/synchromed-II-for-pain/overview/index.htm; accessed June 26, 2009.

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ANESTHESIOLOGY REFLECTIONS

The Cotton-Boothby Apparatus

Drs. Frederic J. Cotton (1869–1938) and Walter M. Boothby (1880–1953) published in 1912 their use of a "bubble bottle" for sight measurement of gas flows. Finally making flow rates and gas proportioning possible, their concept was adopted by Gwathmey in the United States and by Marshall and Boyle in the United Kingdom. The original production model of the Cotton-Boothby Apparatus (above, donated by Cotton to Wood Library-Museum [WLM] Founder Paul Wood) has been continuously displayed at the WLM except from 1977–1987. That decade witnessed an American Society of Anesthesiologists' expansion at Busse Highway that not only demolished the WLM Gallery but also left this venerable apparatus buried under a wooden crate. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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