CASE STUDY

Patient selection and trialing techniques utilizing low-dose intrathecal morphine for chronic nonmalignant pain: A report of two cases

Jay S. Grider, DO, PhD; Michael E. Harned, MD; Paul A. Sloan, MD

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ABSTRACT

The administration of opioid analgesics via the intrathecal route is becoming more commonplace for a variety of chronic nonmalignant pathologic pain states. Despite this growing trend, there is very little information available to guide practitioners with regard to patient selection as well as intrathecal drug dosing paradigms. The authors describe the use of a protocol for patient selection, including pretrial preparation, as well as detailed very low-dose chronic intrathecal morphine dosing regimens to treat patients with refractory chronic nonmalignant pain.

INTRODUCTION

The use of intrathecal analgesic agents for the treatment of chronic nonmalignant pain (CNMP) has become an area of clinical interest over the last three decades.[1,2] CNMP is initially treated using a variety of therapeutic modalities. Initial conservative measures include rehabilitative physical therapy, nonopioid analgesics and adjuvant analgesics, and injective pain therapies. Pain associated with a clear anatomic abnormality such as a herniated nucleus pulposus may require surgery. Many patients, however, are left with moderate-to-severe residual pain that is refractory to standard analgesic treatments. For patients with CNMP refractory to traditional treatments, the use of oral opioids has become more commonplace.[3,4] For patients who have failed all treatment options, including oral opioids (intolerable side effects), intrathecally delivered opioids remain a treatment approach of interest.[5]

Recent guidelines suggest neuraxial opioid trials prior to implantation of a more permanent intrathecal opioid pump[5]; however, there exists a wide variation in the trialing methods described in the literature used to determine patient suitability for long-term intrathecal opioid therapy. Intrathecal opioid trials range from single injection of spinal opioids and evaluation in a physician office (not recommended by the authors) to epidural opioid infusions or to formalized inpatient intrathecal opioid trials over several days.[1] Pretrial psychological evaluation to determine patient suitability is also typically suggested but not mandated. Patients selected for intrathecal opioid infusion should have failed a trial of oral opioids because of inadequate analgesia or intolerable opioid side effects. It is not unusual, however, for oral opioid therapy to be continued during the intrathecal trial or even after implantation of the drug delivery system.[1]

The literature is not clear on what the initial dosing of intrathecal opioids should be.[6] In a review of available studies involving intrathecal opioid analgesia,[1] the dose range of daily intrathecal morphine

varied from 1 to 107 mg/d with an approximate lowest dose range of 2-3 mg/d. This review also commented on the efficacy of intrathecal drug therapy by examining data obtained from several 100 patients followed for several weeks to a maximum of 46 months. The authors concluded that there was a very wide range for average daily doses of intrathecal opioid.[1] Despite the ongoing use of intrathecal opioid therapy, the literature is essentially silent concerning effective initial dosing of intrathecal morphine. This is particularly troubling in light of a very recent publication that highlighted a series of deaths reported within 1 day of intrathecal opioid infusion system implants to treat patients with CNMP.[7] The intrathecal device manufacturers have concluded that patients with CNMP treated with intrathecal opioid therapy experienced increased mortality when compared with similar patients treated with other therapies.[8] It would seem reasonable, therefore, to use the smallest possible dose of intrathecal opioid as initial therapy for patients with CNMP.

These case reports present clinical outcomes for two patients with differing refractory CNMP pathologies and treated with very low doses of chronic intrathecal morphine. These patients demonstrated excellent pain relief with improved physical functioning and required only extremely low doses of intrathecal morphine during a 1-year follow-up period. We present a rationale and a protocol for using low-dose intrathecal opioids to treat chronic and refractory nonmalignant pain based on the concept of low-dose intrathecal morphine therapy.[9]

INTRATHECAL OPIOID PROTOCOL

Patients considered as candidates for intrathecal opioid therapy are (1) gradually weaned off all opioids for at least 6 weeks prior to an intrathecal trial infusion; (2) evaluated by a psychologist prior to trial to identify problematic issues surrounding suitability for catheter implantation; and (3) evaluated by a physical/occupational therapist to establish baseline physical and functional abilities. Candidates without prohibitive mental health problems proceed to an intrathecal morphine inpatient trial.

Under strict aseptic conditions, temporary intrathecal catheters are placed via a low lumbar paramedian approach using local anesthesia and intravenous sedation. Catheters are passed 4-5 cm into the lumbar intrathecal space and tunneled subcutaneously to the lateral flank. Patients are transferred to a designated inpatient ward familiar with intrathecal opioid clinical protocols. The initial intrathecal dose of morphine is 0.025 mg/d delivered via a constant intrathecal infusion pump. The patients' vital signs are monitored every 2 hours. The patients are evaluated three times daily to document efficacy/side effects and adjust intrathecal morphine infusions toward effective analgesia. Primary patient endpoints are clinical pain relief and/or serious side effects that could preclude long-term intrathecal therapy. Intrathecal trials are conducted over approximately 48-96 hours, and morphine infusions are slowly increased until analgesia is achieved or intolerable side effects become apparent. The intrathecal opioid dose is increased every 12 hours as needed until the patient demonstrates functional improvement with acceptable pain control (Numeric Pain Rating Scale (NPS) of 3-4/10). The dosing increments for intrathecal morphine are as follows: Trial day 1 morning, 50 μg/d; evening 100 μg/d; and Trial day 2 morning, 200 μg/d, evening 400 μg/d. Once efficacy is reached at one of the aforementioned doses of intrathecal morphine, the patient continues on that dose for 12-24 hours to observe continued pain relief and evaluate side effects of the medication. Once the therapy has been evaluated, the intrathecal catheter is removed and the patient is discharged after lying supine for 1 hour. Appropriate patients undergo permanent intrathecal drug delivery system implantation within a week.

The following case reports demonstrate application of our intrathecal opioid protocol.

Case 1

Case 1 was a 52-year-old white female with chronic right upper extremity pain diagnosed as Complex Regional Pain Syndrome Type 2 based on results of multiple stellate ganglion and T_2 sympathetic blocks. A variety of clinically ineffective treatments had been tried at an outside clinic including oral opioids, gabapentin, amitryptyline, topiramate, and tiagabine. Spinal cord stimulation successfully controlled her pain. However, the lead anchoring system created pressure ulceration and ultimately the system was explanted. On presenting to our clinic, her pain was described as 8 out of 10 on a NPS. She did not wish to take oral analgesics as multiple trials of oral agents had previously failed. On physical examination, her right upper extremity showed muscular wasting of the thenar eminence as well as the "glassy" appearance of the skin of the left hand. She

experienced allodynia and dysesthesia to light-touch palpation; however, she stated that a vigorous physical therapy program had improved these symptoms. Her passive range of motion at the wrist and elbow was, however, painful. We felt the history, physical examination, and response to sympathetic blocks confirmed the diagnosis of CRPS type 2.

An intrathecal drug delivery system was presented to her as the next available treatment option. Following informed consent and using the aforementioned intrathecal opioid protocol, a percutaneous lumbar intrathecal trial catheter was placed and an infusion of morphine 0.025 mg/d was begun. The patient was admitted to an inpatient ward and instructed to use the painful upper extremity as much as possible. Changes and limits in the patient's physical abilities were evaluated after each change in opioid infusion rate. On trial day 1, the patient stated her pain was 6 out of 10 using the NPS. The infusion rate was incrementally increased to a maximum dose of 0.1 mg/d at the end of day 1. We noted marked improvement in her left upper extremity grip strength, less tactile allodynia, and better tolerance of her activities of daily living. On the morning of trial day 2, the intrathecal morphine infusion was increased to 0.2 mg/d with a further decrease in verbal pain scores to 5/10. The intrathecal infusion was increased to morphine 0.3 mg/d 12 hours later with nearly complete resolution of her pain. She was continued on intrathecal morphine 0.3 mg/d for an additional 24 hours of monitoring. No side effects of intrathecal opioid therapy were noted, and the patient was discharged home after removal of the spinal catheter.

A week later, a SynchroMed (Medtronic's Corp.) intrathecal drug delivery system was implanted and an intrathecal morphine infusion of 0.3 mg/d was initiated. At a follow-up evaluation on postoperative day 10, the patient reported a NPS of 3/10. The patient's pain was well controlled with intrathecal morphine alone and without requiring any supplemental oral opioids. At follow-up 2 years later, her daily intrathecal morphine dose had been titrated modestly upward to 0.41 mg/d with continued good analgesia (NPS reports of pain in the 3-4/10 range) and improved participation in activities of daily living.

Case 2

Case 2 was a 62-year-old white female with a history of chronic low back pain not relieved by nonsteroidal anti-inflammatory drugs, physical therapy, or surgical treatments. Her previous surgery included a lumbar microdiscectomy at L4-5 and L5-S1, as well as a spinal fusion from L3 to S1. There was no radicular component to her pain, which was reported as 9/10 on a NPS. She was taking hydrocodone 7.5 mg/acetaminophen 500 mg three times daily over the previous 2 years with diminishing analgesic efficacy and coupled with side effects of sedation and constipation. The referring surgeon had requested medial branch blocks above and below the level of the spinal fusion with the idea that radiofrequency denervation of the facet joints might help to reduce the pain. Because of the degree of scarring encountered around the fusion site, it was determined that radiofrequency denervation would be technically difficult and most likely not helpful. Her hydrocodone administration was tapered, and other oral opioids (methadone, morphine, and oxycodone) were tried and discontinued because of intolerable side effects. Thus, a trial of intrathecal morphine was initiated using the above intrathecal opioid protocol.

On day 1 of the trial, the patient reported pain (NPS of 8/10) while receiving a morphine infusion of 0.025 mg/d. During trial day 2, the morphine infusion was increased to 0.05 mg/d and subsequently to 0.075 mg/d with a decrease in pain (NPS of 5/10) and increased activity level. By the end of the trial day 3, the patient's intrathecal morphine dose had been increased to 0.150 mg/d, resulting in excellent pain relief (NPS of 2/10) and increased functional capacity. No limiting side effects were apparent, and a SynchroMed intrathecal infusion system was implanted the following week according to protocol.

The patient was treated with intrathecal morphine infusion alone for over a year without side effects and required only a small dose escalation to 0.258 mg/d to maintain acceptable pain relief (NPS of 3-5/10). The patient experienced significant pain relief even during her activities of daily living with her only complaint being pain in the morning on awakening. An apparent diurnal variation in pain relief was recognized and treated by slightly increasing the morning intrathecal morphine dose. At 2-year follow-up, the patient continued to report excellent pain relief (NPS of 3/10) with the dose of intrathecal morphine maintained at 0.258 mg/d and with improved activities of daily living.

DISCUSSION

Since intrathecal drug delivery systems were first used 25 years ago for the infusion of analgesic

agents to treat CNMP, it has been recognized that patient selection and trialing techniques would be a key component to the success of the therapy.[10] Perhaps, the first discussion concerning guidelines for trials of chronic intrathecal opioids was from Krames.[11,12] These early guidelines outline the vast array of trial methods, most of which are still in use today. We report the successful trialing technique of ultra-low-dose intrathecal morphine dosing for the treatment of CNMP. To our knowledge, this technique has not been previously described. Both our patients achieved good pain relief with a daily dose after 2 years of infusion of intrathecal morphine less than 0.3 mg/d, less than the lowest recorded intrathecal dosing in the literature.[1]

Screening techniques for chronic spinal opioid therapy currently in practice today can be broadly categorized into either the epidural or intrathecal route of administration, coupled with one of the following delivery modalities: (1) single-shot injection, (2) multiple injections, or (3) continuous infusion.[1] We prefer an inpatient intrathecal continuous infusion route as outlined in the aforementioned protocol. The single-shot technique is often performed in the physician's office as a single-day trial. Advantages of the single-shot technique are a relatively noninvasive method of delivering the opioid that is less time consuming for the patient. The multiple injection route, also usually done in office, allows for a placebo dose to be administered for comparison with true opioid administration. However, continuous infusion more closely mimics the experience that the patient will have with a chronic opioid delivery system. Outpatient continuous infusion allows the patient to experience therapy while undergoing their daily routine in their own familiar environment but does not allow close patient monitoring. An inpatient continuous infusion allows rapid titration of the opioid dose while closely monitoring for side effects. The intrathecal route of delivery also more closely mimics the implanted drug delivery route, and thus making it preferable to epidural administration. Additionally, it has been suggested that the best way to limit the placebo response is to extend trials as long as logistically possible making the single- and multiple-shot routes less attractive.[13] Because of these factors we strongly recommend an inpatient intrathecal continuous infusion route, as outlined in the current protocol.

Although the administration of intrathecal opioids has been described since the early 1980s, the doses of morphine used were significantly higher than those used in our two cases.[1,14] From a review of 22 intrathecal opioid studies,[1] the lowest reported daily morphine doses were 0.5 mg/d[15] and 1 mg/d.[16] Dosages of 5-10 mg/d have been commonly reported,[1] with many of these patients also concomitantly on oral opioids. In a review from 2002, Wallace and Yaksh[1] suggested that an appropriate starting dose for intrathecal therapy would be in the 0.5-1.0 mg/d range, with higher doses often required for patients receiving chronic opioid therapy. In our current intrathecal opioid protocol, following a 6-week opioid-free interval, patients receive only 0.025 mg/d of intrathecal morphine as an initial dose. This is very important for patient safety as almost all case reports of death following initiation of intrathecal opioids were reported with daily doses of morphine 1 mg or higher.[7] Every 12 hours the morphine dose for our patients is adjusted by 50 percent based on reported pain score, functional assessment by physical and occupational therapy, and side effects experienced. Of our two reported cases, the range of the final intrathecal morphine doses were only 0.2-0.25 mg/d, significantly lower than any previously reported ranges.

A limited number of studies suggested that low-dose administration of opioids may be associated with the phenomena known as opioid-induced hyperalgesia.[17-20] These anecdotal reports described a biphasic response to morphine in which some patients became hyperalgesic to painful heat challenge in lower dose ranges but experienced pain relief at higher dosages.[21] Conversely, at least one acute pain report suggests that low-dose intrathecal opioid agonists may have dramatic analgesic effects.[22] Blay et al.[22] demonstrated that low-dose intrathecal morphine administered preoperatively significantly improved postoperative pain scores. In this study, intrathecal administration of 0.2 mg of morphine essentially eliminated the need for postoperative intravenous morphine for the first 24 hours. Moreover, the analgesic effect of the intrathecal morphine continued throughout the 48-hour trial period. In this study, minimal supplemental morphine postoperatively was required, and improved visual analog pain scores were reported in the intrathecal morphine group.[22]

It is likely that the effective analgesia seen in our patients with ultra-low-dose intrathecal morphine and the similar analgesic effect described by Blay et al. are linked to the opioid-free interval. Our protocol requires that patients gradually taper and completely

wean from all opioid therapy for at least 6 weeks prior to the low-dose intrathecal morphine trial. We suggest that this opioid holiday allows a return to a normalized state of pharmacology in the dorsal horn of the spinal cord. A return to the opioid receptor native state in turn allows for increased opioid efficacy using our much lower doses. An analogous clinical scenario is in the opioid-naive patient who presents for surgery. Blay et al.[22] used 0.2 mg of single-dose morphine intrathecally prior to induction of general anesthesia for abdominal aortic surgery. This dose, similar to those used in our cases, was found to significantly decrease postoperative morphine requirements for up to 48 hours.[22]

Our small case series using this intrathecal opioid protocol suggests that it may be possible to obtain a resetting of the intrathecal opioid system to a baseline native state following a drug holiday. In most published intrathecal opioid studies, oral opioid administration has not been typically discontinued and, in fact, has often been used in combination with intrathecal administration of spinal opioids. To extrapolate from the current literature, the continuation of oral analgesics in the opioid-tolerant patient may decrease the efficacy of intrathecal morphine, whereas our protocol seems to provide an opportunity for enhanced analgesia. Additional studies are underway at our institution to better understand the role of low-dose intrathecal opioids in the management of chronic pain.

To our knowledge, dose-response studies for intrathecal morphine have not been conducted in humans. The available literature suggests that the lower end of the intrathecal morphine analgesic effects may extend into the microgram per day range in opioid-naive subjects. Our observations suggest that the lower limits of effective intrathecal morphine doses may lie in the 50 μg/d range. This practice is compatible with recent advice to initiate intrathecal opioid therapy using the lowest possible dose that will provide analgesia.[23] Our patients reported clinically significant relief within this dose range with maximum efficacy occurring at a dosage of 0.25 mg/d of intrathecal morphine. These findings also suggest that it may be possible to establish an intrathecal dose-analgesic response relationship for opioid agonists using this paradigm. Additional studies are clearly required to more fully examine the possibility that the dose-response relationship in opioid-free humans may be shifted to the left of the current dosing regimens.

In conclusion, these initial case reports suggest that an intrathecal opioid protocol incorporating a pretrial opioid holiday may allow clinically significant pain relief, with improved functional abilities, at very low doses of daily intrathecal morphine. Currently, studies are ongoing to establish (1) intrathecal opioid dose-analgesic response relationships, (2) long-term stability, efficacy, and safety of this intrathecal opioid protocol, and (3) novel applications of this technique across pain syndromes of varying etiologies.

Jay S. Grider, DO, PhD, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

Michael E. Harned, MD, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

Paul A. Sloan, MD, Department of Anesthesiology, University of Kentucky, Lexington, Kentucky.

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