Case Report

Respiratory Failure Following Delayed Intrathecal Morphine Pump Refill: A Valuable, but Costly Lesson

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Background: Spinal analgesia, mediated by opioid receptors, requires only a fraction of the opioid dose that is needed systemically. By infusing a small amount of opioid into the cerebrospinal fluid in close proximity to the receptor sites in the spinal cord, profound analgesia may be achieved while sparing some of the side effects due to systemic opioids. Intraspinal drug delivery (IDD) has been increasingly used in patients with intractable chronic pain, when these patients have developed untoward side effects with systemic opioid usage. The introduction of intrathecal opioids has been considered one of the most important breakthroughs in pain management in the past three decades. A variety of side effects associated with the long-term usage of IDD have been recognized. Among them, respiratory depression is the most feared.

Objective: To describe a severe adverse event, i.e., respiratory failure, following delayed intrathecal morphine pump refill.

Case Report: A 65-year-old woman with intractable chronic low back pain, due to degenerative disc disease, and was referred to our clinic for an intraspinal drug delivery evaluation, after failing to respond to multidisciplinary pain treatment. Following a psychological evaluation confirming her candidacy, she underwent an outpatient patient-controlled continuous epidural morphine infusion trial. The infusion trial lasted 12 days and was beneficial in controlling her pain. The patient reported more than 90% pain reduction with improved distance for ambulation. She subsequently consented and was scheduled for permanent intrathecal morphine pump implantation. The intrathecal catheter was inserted at right paramedian L3-L4, with catheter tip advanced to L1, confirmed under fluoroscopy. Intrathecal catheter placement was confirmed by positive CSF flow and by myelogram. A non-programmable Codman 3000 constant-flow rate infusion pump was placed in the right mid quandrant between right rib cage and right iliac crest. The intrathecal infusion consisted of preservative free morphine, delivering 1.0 mg / day. Over the following 6 months, the dosage was gradually titrated up to 4 mg/day with satisfactory pain control without significant side effects. However, the patient was not able to return to the clinic for pump refill until 12 days later than the previously scheduled pump-refill date. Her pump was accessed and was noted to be empty. Her intrathecal pump was refilled with preservative free morphine, delivering 4 mg/day (the same daily dose as her previous refill). However, on the night of pump refill, 10 hours after the pump refill, the patient was found to be unresponsive by her family members. 911 was called. Upon arriving, paramedics found her in respiratory failure, with shallow breathing at a rate of 5/min, pulse oxymetry showing oxygen saturation about 55-58%. She was emergently intubated on site and rushed to local hospital ER. The on call physician for our clinic was immediately contacted, and advised the administration of intravenous Naloxone. Her respiratory effort improved dramatically after receiving a total of 0.6 mg IV Naloxone IV over 25 minutes. Her intrathecal pump was immediately accessed by clinic on call physician and the remainder of the medication in the catheter space was aspirated. The pump infusate was immediately diluted with preservative free normal saline, to deliver preservative free morphine at 1mg/day. She was transferred to the intensive care unit and extubated the next morning. She recovered fully without any sequelae.

Conclusion: Loss of opioid tolerance due to delayed pump refill may subject patients to the development of severe respiratory depression. Meticulous approach should be employed when refilling pumps in these patients when their pumps are completely empty. To our knowledge, this is the first reported case of this type.

Key words: intraspinal drug delivery pump, intrathecal morphine, respiratory depression, opioid tolerance

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Intraspinal drug delivery (IDD) of opioid, via an implanted pump and catheter, is increasingly used in a subset of patients with intractable chronic pain, who have failed to respond to conventional treatment or can not tolerate systemic opioid due to side effects (1-5). Morphine, the only FDA-approved opioid for intrathecal administration, is most commonly used for this purpose. Although morphine is effective, inexpensive and well tolerated by the majority of patients, along with the increasing utilization of intrathecal morphine for intractable chronic pain, more and more clinically relevant side effects have become evident (6,7). Side effects with long-term intraspinal morphine infusion may include pruritis, nausea, vomiting, constipation, fluid retention, sexual dysfunction, urinary retention and respiratory depression (6,7). Respiratory depression is the most feared side effect of intraspinal opioid therapy.

Prior to the permanent intrathecal pump implantation, an intraspinal analgesic infusion trial is required to document efficacy of IDD therapy. In general, if the patient reports ≥50% pain reduction with improved function, the trial is considered to be a "positive trial" and a permanent intrathecal infusion pump may be in order. Pain relief that is < 50% or the development of intolerable side effects constitutes a "negative trial" (1).

Case Report

A 65-year-old woman with intractable chronic low back pain, due to degenerative disc disease, was referred to our clinic for an intraspinal drug delivery evaluation, after failing to respond to multidisciplinary pain treatment. Following a psychological evaluation confirming her candidacy, she underwent an outpatient patient-controlled continuous epidural morphine infusion trial. A tunneled lumbar epidural catheter was placed at L4-L5, with catheter tip advanced to L2, under fluoroscopic guidance. Satisfactory catheter placement was confirmed by epidurogram. The proximal tip of the catheter was then tunneled, subcutaneously and connected to a Microject™ PCEA (patient-controlled epidural analgesia) pump (Codman, Raynham, MA, USA) and a reservoir bag containing preservative free Morphine at a concentration of 0.4 mg/mL. The pump was programmed to deliver a basal rate of 0.5 mL/hr, with the on-demand bolus dose of 0.2 mL, and a lock out interval of 60 minutes. The patient was then instructed how to use the pump and was discharged home. During the trial, the infusion rate was further increased to 1.1 mL/hr with the on-demand bolus dose increased to 0.4 mL. The patient did require using the on-demand bolus dose, averaging about 4-5 times/day. The patient was receiving approximately 11 mg epidural morphine daily (infusion of epidural morphine solution (conc. 0.4 mg/mL) at 1.1 mL/hr x 24 hrs plus 5 x on-demand boluses of 0.4 mL. The infusion trial lasted 12 days and was beneficial in controlling her pain. The patient reported more than 90% pain reduction with improved distance for ambulation. She did experience initial transient, mild itching that completely resolved. She did not experience any other significant adverse events during this epidural morphine infusion trial. She subsequently consented and was scheduled for permanent intrathecal morphine pump implantation. The intrathecal catheter was inserted at right paramedian L3-L4, with catheter tip advanced to L1, confirmed under fluoroscopy. Intrathecal catheter placement was confirmed by positive CSF flow and by myelogram. A non-programmable Codman 3000 constant-flow rate infusion pump was placed in the right mid quandrant between right rib cage and and the right iliac crest. The initial intrathecal infusion consisted of preservative free morphine, delivering 1.0 mg/day. Over the following 6 months, the dosage was gradually escalated to 4 mg/day with satisfactory pain control without significant side effects. However, due to an unexpected family situation, the patient was not able to return to the clinic for pump refill; nor was she able to be reached by our clinic staff as she had been out of town. She came in 12 days later than the previously scheduled pump-refill date. Her pump was accessed and was noted to be empty. Her intrathecal pump was refilled with preservative free morphine, delivering 4 mg/day (the same daily dose as her previous refill). No bridge bolus was attempted. However, on the night of pump refill, 10 hours after the pump refill, the patient was found to be unresponsive by her family members, associated with shallow, slowed breathing. 911 was called. Upon arriving, paramedics found her in respiratory failure, with respiratory rate of 5/min, pulse oxymetry showing oxygen saturation about 55-58%. She was emergently intubated and rushed to local hospital ER. The on call physician for our clinic was immediately contacted, and advised by phone the administration of 0.1 mg of Naloxone intravenously (IV), repeat as needed. Over the next 25 minutes as the IV Naloxone was administred,her responsiveness and alertness started to improve after receiving 0.4 mg and her respiratory effort imorved dramatically after receiving a total of 0.6 mg. While she was still intubated, her intrathecal pump was immediately accessed by the clinic on call physician

and the remainder of the medication in the catheter space was aspirated. The pump infusate was immediately diluted to deliver preservative free morphine 1 mg/day. She was transferred to the intensive care unit and extubated the next morning. She recovered fully without any sequelae.

Discussion

Respiratory depression is rare in patients receiving chronic opioid therapy. It tends to occur in opioid naïve patients following acute administration of an opioid (8). Opioid induced side effects may develop regardless of the route of drug administration (9,10). Intraspinal opioid therapy has also been associated with other complications such as respiratory depression (11). Clinically important respiratory depression has been reported following intrathecal (12) and epidural morphine (13) and other opioids (7). Intraspinal opioid induced respiratory depression is divided into 2 types: early respiratory depression which occurs within 2 hours of injection of the opioid; delayed respiratory depression which occurs more than 2 hours after opioid administration (7). Most reports of the early types involve epidural administration of Fentanyl or Sufentanil (7). They are thought to be mostly due to systemic absorption of the drugs, as blood concentration of the drugs has been found to be proportional to the magnitude of respiratory depression (14,15). Early respiratory depression due to intrathecal morphine administration has never been reported. In contrast, all reports of clinically relevant delayed respiratory depression have involved the administration of morphine, either intrathecally or epidurally (12). However, there is a paucity of reports in the literature on delayed respiratory depression caused by long-term intrathecal morphine therapy. Delayed respiratory depression results from cephalad migration of the opioid in the cerebrospinal fluid and subsequent interaction with the opioid receptors located in the ventral medulla (8,16). Delayed respiratory depression usually occurs 6-12 hours following intrathecal or epidural morphine administration. As a matter of fact, there has been only one published report in the literature on delayed respiratory depression caused by long-term intrathecal morphine therapy, in which a 41-year-old male, with severe neuropathic upper extremity pain due to brachial plexopathy, developed progressive deterioration of his pulmonary status, ie, respiratory acidosis and bradypnea with gradual escalation of intrathecal morphine dosage over the one year period of time, finally improved following morphine dose reduction (17). Pharmacologically, opioid tolerance (to analgesia) is defined as the loss of analgesic effect of an opioid during a period of time at constant dose (18). Tolerance represents a need to increase the opioid dose to achieve the same effect or it represents a diminished effect for the same dose of opioid. The mechanisms that lead to tolerance are complex and have yet to be fully understood. It is thought to involve the N-methyl-D-aspartate (NMDA receptor) (10,19,20). In contrast, opioid tolerance to side effects refers to the presence of analgesia and absence of side effects while on opioid therapy. It develops at different rates for different effects. Tolerance to nausea, vomiting, and sedation occurs rapidly, while tolerance to constipation and miosis develops very slowly, if at all (10). In clinical practice, "opioid-tolerant" is used to describe patients who are taking strong opioids (the daily equivalent of 60 mg oral morphine or 25 mcg/hr transdermal fentanyl) and thus presumed to be tolerant to opioid induced adverse effects (9). There is no literature, however, to define how much intrathecal daily morphine should be considered as "opioid tolerant".

In our case, the patient was opioid-tolerant (on extended morphine 60 mg twice/day) prior to the pump implantation. Following pump placement, the intrathecal morphine dosage gradually increased to 4 mg/day over a 6-month period of time. She was experiencing satisfactory pain relief at this dose without any side effects. We assumed that intrathecally 4 mg/day would still qualify her as opioid-tolerant based on the commonly used conversion method of intrathecal morphine:oral morphine of 1:300 (1). However, our patient missed pump refill appointment by 12 days which meant that her pump had been empty for about 7-8 days as she had a "leeway" of 3-4 days from the scheduled the pump refill date. Yet, the patient developed respiratory failure requiring emergent intervention. We speculate that the exhaustion of her intrathecal morphine for one week abolished her "opioid tolerant" status and rendered her "opioid naïve" which induced her respiratory depression.

We had speculated that the incidence of serious adverse events such as respiratory depression, respiratory failure, or even respiratory arrest was higher than what appeared in the literature, as we felt that not all cases of such were reported. Our case event happened in July 2006; we started our preparation for writing this case report in August, 2006; submitted to "*Pain Physician*" in May 2007 and it was accepted for publication in September 2007 (Decision Letter 07-041). However, based on the recommendation of our legal advisors we

decided to postpone consideration for publication for 2 years and we reluctantly withdrew the accepted manuscript in October 2007.

In November 2006, when this manuscript was still in preparation, Medtronic sent out an "Educational Brief" to selected implanting physicians who implant Medtronic Synchromed[R] and Isomed[R] infusion pumps. This "Educational Brief" informed physician implanters that Medtronic had received reports of 9 patient deaths between December 2005 and March 2006, happening within 3 days after initiation or re-initiation following interrupted use of intrathecal opioid therapy for pain. The cases involved new system implants, catheter revisions, and system replacement. Medtronic conducted a thorough investigation and concluded that device malfunctioning was not the cause of those adverse events, but opioid overdose and/or sedative overdose were.

Since this incidence of the adverse event, we have taken painstaking measures to make sure that patients do not miss their pump refill appointments. We have also expanded the "leeway" of pump refill from about 3-4 days (previously) to 7-10 days. For any missed pump refill, we restart their intrathecal pump infusion at minimal dose (0.5mg to 1mg morphine equivalent) and caution patients, and their family members to watch for symptoms of over-sedation and respiratory depression. We have not had any recurrent event since.

Surprisingly, it was only recently (October 2009), 3 years later following the Medtronic's "Educational Brief," that Coffey at al (21) published an article based on the observation of a cluster of 3 deaths in 2006, happening within one day following intrathecal opioid pump implantation for noncancer pain. After analyzing 9 index cases (3 sentinel cases and 6 others by prospective strategy), the authors concluded that increased mortality may exist in patients treated with intrathecal opioid therapy for noncancer pain, with presumed respiratory arrest caused by or contributing to the deaths of the patients, although the exact causes of deaths, and the proportion attributable to intrathecal opioid administration remained to be determined.

Conclusion

Extreme caution should be practiced in refilling empty intrathecal morphine pumps as dreadful respiratory failure may occur due to the loss of opioid tolerance to side effects.

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