Pain Physician 2008; 11:3:363-367 • ISSN 1533-3159

Case Report

Severe Peripheral Edema During an Outpatient Continuous Epidural Morphine Infusion Trial in a Patient with Failed Back Surgery Syndrome

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Disclaimer: There was no external funding in preparation of this manuscript.
Conflict of interest: None

Manuscript received: 11/28/2007
Revised manuscript received: 01/15/2008
Accepted for publication: 02/05/2008

Background: Intraspinal drug delivery therapy has been increasingly used in patients with intractable, nonmalignant pain who fail to respond to conventional treatment or cannot tolerate systemic opioid therapy due to side effects. By infusing small amount of analgesics directly into the cerebrospinal fluid in close proximity to the receptor sites in the spinal cord, one is able to achieve the spinally mediated analgesia, sparing side effects due to systemic opioids. Prior to permanent intraspinal pump implantation, an intraspinal opioid screening trial is required to document the efficacy of intraspinal opioid for analgesia. Although there are a few approaches in conducting such screening trials, a patient controlled continuous epidural morphine infusion trial, performed in an outpatient setting, is widely accepted by many interventional pain specialists. The major advantage of conducting an outpatient trial is that it mimics what patients do in their daily living, therefore minimizing the false positive rate.

Objective: To report a case of severe peripheral edema observed during an outpatient continuous epidural morphine infusion trial.

Case Report: A 64-year-old female, with a 7-year history of severe low back pain and bilateral leg pain due to failed back surgery syndrome, was referred to our clinic for intraspinal drug delivey therapy after failing to respond to conservative treatment, including a previous history of 3 lumbosacral surgeries. Following a pre-implantation psychological evaluation confirming her candidacy, she underwent an outpatient patient-controlled continuous epidural morphine trial.

A tunneled lumbar epidural catheter was placed at L2-L3 with catheter tip advanced to T12 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 pump (Codman, Raynham, MA, USA) and reservoir bag containing preservative-free morphine 0.5 mg/mL. The pump was programmed to deliver a basal rate of 0.5 mL/hr. The bolus dose was 0.2 mL with 60 minute lock-out interval. The patient was instructed how to operate the infusion pump before discharging home. During the following 2 weeks, she reported more than 90% reduction of her low back and leg pain. She only had to use the on-demand bolus doses averaging 2 – 3 times a day. She was able to wean off her oral opioids completely. However, she developed bilateral leg edema and gained over 12 pounds during the 2-week infusion trial, despite wearing elastic stockings and keeping her legs elevated whenever possible. She did not experience any other significant side effects. Her edema finally resolved 2 days after termination of the epidural infusion.

Conclusion: Peripheral edema may occur and persist during epidural morphine infusion. This report represents the first case report, to the best of our knowledge, describing severe peripheral edema in an otherwise healthy patient while on epidural morphine administration during an outpatient epidural morphine infusion trial. This case report shows that continuous epidural morphine infusion, even in small dose, may cause peripheral edema in some patients.

Key words: Epidural morphine infusion trial, intraspinal drug delivery pump, failed back surgery syndrome, methadone, peripheral edema

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Intraspinal drug delivery pump therapy has been increasingly utilized in patients with intractable, nonmalignant pain (1-5). It is well accepted that a temporary trial of intraspinal analgesia be conducted to document efficacy prior to the implantation of a permanent intrathecal drug delivery pump (1). A patient-controlled continuous epidural opioid infusion trial, conducted on an outpatient basis, is one of the approaches chosen by many interventionists (6) including the authors. It consists of inserting a flexible epidural catheter under fluoroscopic guidance; tunneling the catheter subcutaneously, and reconnecting it with Microject PCEA infusion pump (7,8). The pump is programmed by the physicians to deliver selected analgesics, mostly an opioid (e.g., morphine) with or without local anesthetics (e.g., bupivacaine), in a continuous fashion, with an on-demand bolus button accessible to the patient. The patient is discharged home to resume his or her usual activities of daily living. In our clinic, the outpatient infusion trial spans 1 – 2 weeks. The oral opioids are usually weaned off during the trial. More than 50% pain reduction together with demonstrable improved functional level during trial is generally considered a positive trial (1).

Case Report

An otherwise healthy, 64-year-old female (5'3", 121 lbs), was referred to our pain clinic for intraspinal drug deliver therapy. The patient had a 7-year history of severe low back pain and bilateral leg pain due to degenerative lumbar disc disease, lumbar spinal stenosis, and lumbar radiculitis. The patient also had a previous history of 3 lumbosacral surgeries, with the last one being lumbar fusion at L3-L4, L4-L5, and L5-S1 about 2 years ago, after she had tried multimodality treatment including medication trials, physical therapy including transcutaneous nerve stimulation (TENS), numerous spinal interventional treatments including epidural steroid injections, lumbosacral transforaminal steroid injections, lumbar facet blocks, and lumbar facet radiofrequency rhizotomy, without long-term benefit. The patient described her low back pain being equally bothersome to her bilateral leg pain. Her pain level was usually at 8 – 9/10 on numerical pain scale of 0 – 10, even with her medications. Her low back pain generally worsened by sitting while her bilateral leg pain, which was described as starting from both buttocks down to the bilateral posterior thigh, extending further down to the posterior calves and then to the bottom of her feet, significantly worsened by walking, standing, and any kind of activity. She was without any significant past medical history of cardiac, hepatic, renal, vascular, or endocrine diseases. Nor did she have previous history of venous stasis or leg edema of any type. Her only past surgical history included 2 previous C-sections and 3 lumbar surgeries. She had no history of alcohol, cigarette, or illicit drug usage. She had been a housewife since her marriage at age 18. Her family history and review of systems were non-contributory. Her medications included methadone 40mg bid, hydrocodone/acetaminophen 10/500 qid as needed, gabapentin 600mg qid, and baclofen 10mg qhs. She had been on these drugs for over 3 months. Further methadone dose escalation was associated with profuse sweating. She had previously tried other long acting opioids including oral morphine, oxymorphone, oxycodone, and trans-dermal Fentanyl patch, prior to coming to our clinic, but without efficacy. Her lumbar MRI with and without contrast showed post surgical changes of the lumbar spine including paraspinal fixation rods from L3 through S1 and post decompressive laminectomy at L3-L4, L4-L5, and L5-S1.

Since she was referred to our clinic for IDD therapy, after she had failed to respond to all other multidisciplinary pain treatments offered elsewhere, and because of the severity of her back and leg pain (8 – 9/10 on a numerical pain sale), it was decided that she be prepared for intraspinal drug delivery therapy without further delay. After passing a pre-implantation psychological evaluation confirming her candidacy, she underwent an outpatient patient-controlled continuous epidural morphine trial. A tunneled lumbar epidural catheter was placed at L2-L3 with the catheter tip advanced to T12 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 pump (Codman, Raynham, MA, USA) and reservoir bag containing preservative free morphine 0.5 mg/mL. The pump was programmed to deliver a basal rate of 0.5 mL/hr. The bolus dose was 0.2 mL with a 60-minute lock-out interval. The patient was instructed how to use the pump properly as well as how to gradually wean off her oral methadone before discharging home. During the following 2-week outpatient morphine infusion trial, she reported a more than 90% reduction of her low back and leg pain. Her epidural morphine infusion dose remained the same during the entire trial period. She only had to use the

on-demand bolus doses averaging 2-3 times a day. She was able to wean off her oral methadone completely. However, she noticed bilateral leg edema on the fourth day following the initiation of patient-controlled epidural analgesia (PCEA) infusion. The edema progressively worsened, extending from her bilateral feet to mid calves, despite wearing elastic stockings and keeping her legs elevated whenever possible, as recommended. She gained over 12 pounds at the end of the 2-week infusion trial. She did not experience any other significant side effects besides leg edema and, her low back and leg pain lessened dramatically (90% pain reduction) during the epidural morphine infusion trial.

Discussion

Systemic opioids may cause peripheral edema (9, 10). Gardner-Nix (9) reported 5 cases of peripheral edema due to systemic opioids in patients with non-maligmant pain; 2 with a trans-dermal fentanyl patch; 2 with morphine, and one with methadone. Interestingly, of the 2 patients on oral morphine who developed edema, one did so when the morphine dosage was slowly escalated to 400mg every 8 hours, while the other one noticed pedal edema when morphine dosage was gradually increased up to 120mg every 8 hours and short acting morphine 25mg 3 times daily was added as needed for breakthrough pain. Prior to reaching the above mentioned dosage, there was no edema noted by the patients or physicians. Obviously, the daily morphine dosages in the above cases, that precipitated leg edema, were quite large (435 – 1,200mg/day).

Multiple studies have shown that systemic morphine can cause histamine release (11-14), which may, in turn, contribute to peripheral edema. Grossmann et al (13) have successfully demonstrated that the venodilatory effect of morphine is mediated by histamine release, and the venodilation is morphine dose-dependent. Opioid mu receptors have little or no role in the process of venodilation. This conclusion was compatable with what Gardner-Nix (9) observed, that edema tended to occur when the oral morphine dosage was escalated to certain levels.

Our patient, however, received epidural morphine infusion at 6.3 mg/day (conc: 0.5mg/mL infused at 0.5 mL/hr, avg. 3 boluses 0.2 mL/day), during the 2-week epidural infusion trial and developed progressive lower extremity edema, unresponsive to conventional maneuvers such as leg elevation and wearing elastic stockings. Morphine-induced histamine release was unlikely to be the underlying mechanism because of the minute dose in comparison to the systemic doses in the cases above. Therefore, a centrally mediated mechanism is speculated.

Increased vasopressin release from the posterior pituitary induced by opioid, a working hypothesis initially proposed by de Bodo (15) and subsequently by Bisset et al (16), was widely accepted to account for peripheral edema due to centrally administered opioid (17), although a few animal studies showed conflicting results in terms of vasopressin release to intraspinal morphine, increasing in some reports (18,19), decreasing in others (20,21). However, most of the animal studies done investigated vasopressin release following acute morphine administration up to 24 hours. To the best of our knowledge, the literature lacks such studies investigating intraspinal opioid infusion on vasopressin release beyond 24 hours, preferably up to 2-weeks or even longer. Our speculation is that prolonged intraspinal opioid infusion may show a more consistent response of increased vasopressin release although this hypothesis needs further verification. Recall that our patient started to develop leg edema on the fourth day during the 2-week epidural morphine infusion trial.

Nevertheless, some researchers believe that opioid-induced vasopressin release alone is an over-simplified view, and therefore inadequate to explain opioid-induced antidiuresis. Indeed, Huidobro-Toro and Huidobro (22) first observed striking differences in urine electrolytes in rats following intraventricular injection of antidiuretic hormone and opioids respectively, the former being oliguria with high concentration of Na+ and K+ , while the latter being a very low concentration of urine electrolytes, suggesting opioids selectively activate central opioid receptors to produce changes in urine formation and composition. This hypothesis was further substantiated by Danesh and Walker (23) through their demonstration that central administration of morphine in conscious rats enhanced renal tubular sodium re-absorption, the antinatriuretic effect, by an opiate receptor-dependent mechanism. Further, they proposed that systemic opioids may act via an effect on the central nervous system, at either spinal or supraspinal levels, to modify renal function, although the exact mechanisms need further characterization. The opioid receptor involved, based on evidence so far, pointed to mu-type responses (23).

It is noteworthy that our patient, obviously with opioid tolerance (on methadone 40mg twice daily and hydrocodone 10mg 4 times daily as needed prior to the infusion trial), did not develop any peripheral edema while on the oral regimen of the above. This could not be explained by either the histamine release mechanism (13) or centrally mediated renal modulating mechanism of systemic opioids (23) as proposed by Danesh and Walker. We speculate that there could be some type of threshold point or dosage above which events mediated through the above mechanisms would occur. Interestingly, Gardner-Nix (9) reported that a patient with nonmalignant pain developed severe leg edema while on methadone 480mg daily.

While on a comparatively much smaller dosage scale of continuous epidural morphine infusion, i.e., 6.3mg/day, our patient developed severe, progressive peripheral edema, with a weight gain of over 12 pounds during the 2-week trial, suggesting that the antidiuretic effect of epidural morphine was more profound than systemic methadone, which appeared to be the case in our patient. This becomes more interesting when one considers that the continuous epidural morphine infusion at 6.3mg/day caused severe leg edema, yet long-term oral methadone usage of 80mg/day did not do so in the same patient, especially in view of the commonly recommended equianalgesic conversion ratio of methadone:morphine being anywhere from 1:3 to 1:20 depending on the total oral morphine dose (24).

Peripheral edema has also been increasingly recognized as a problematic side effect with chronic intrathecal morphine infusion therapy (17,25-28). Aldrete and Couto (25) reported 5 cases of leg edema in 23 patients on long-term intrathecal opioids (3 on oxymorphone 6 – 13 mg/day, 2 on morphine 12 – 16 mg/day). The authors attributed the development of leg edema to previous leg edema and venous insufficiency, exacerbated by opioid dose-dependent vasodilation, and therefore concluded that "Pre-existing leg venous insufficiency and edema may be relative contraindications for the continued use of intrathecal opioids in patients with chronic pain" (25).

Anderson et al (26) reported, in their retrospective study of 37 patients on long-term intrathecal opioid therapy, 16% of the patients developed problematic leg edema while on intrathecal morphine infusion. Switching to intrathecal hydromorphone only transiently improved the leg edema. There was no mention in the report whether any of the patients who developed leg edema had pre-existing edema or venous stasis. The authors also seemed to believe the interaction of opioid analgesics with the pituitary hormonal regulatory system (leading to the release of vasopressin from the posterior pituitary), to be the underlying mechanism (17). Again, as discussed above, some researchers believed that opioid-induced vasopressin release alone was an over-simplified view, and inadequate to explain opioid-induced antidiuresis (22,23). Furthermore, the demonstration of enhanced renal sodium re-absorption in rats following a centrally administered opioid, by Danesh and Walker (23), suggested a centrally mediated renal modifying mechanism.

It is puzzling, yet fortunate, that only a small percentage of patients (6.1 – 21.7%) on intrathecal opioid therapy develop leg edema (25-27), with the highest percentage (21.7%) being reported in patients having pre-existing leg edema or venous stasis (25). It seems reasonable to believe the suggestion by Aldrete and Couto (25) that the pre-existing conditions such as edema and/or venous stasis predisposed patients to the development of leg edema, although the exact mechanism may not be what they speculated as opioid dose-dependent vasodilation. Studies in patients without any of the above mentioned pre-existing conditions, yet with the development of edema, are needed in order to further substantiate this hypothesis and to further explore the exact underlying mechanism.

Our case, however, is different in that the patient received continuous epidural morphine infusion instead of intrathecal infusion. There have been no previous reports in humans, to the best of our knowledge, describing the development of leg edema while on continuous epidural morphine infusion, especially in the setting of an outpatient epidural infusion trial. Furthermore, our patient is an otherwise healthy female without any known medical history of hepatic, renal, cardiac, endocrine, or vascular diseases. The development of severe, progressive leg edema during the 2-week epidural morphine infusion trial in our patient, who had no previous history of leg edema or venous stasis, prompted us to describe this case report, re-examine the seemingly known pathogenesis of this complication, and hopefully and most importantly, to stimulate some research interest and effort from other clinicians/scientists, in search of a more specific treatment. This is important because we will no doubt be dealing with this complication a lot more often because of the increasing popularity of IDD pumps for both malignant and nonmalignant pain.

We believe that the peripheral edema associated with epidural or intrathecal morphine infusion shares a similar mechanism, which probably involves centrally mediated events including both vasopressin release and urine composition alteration.

Conclusion

Peripheral edema may occur and persist during continuous epidural morphine infusion therapy. This case report shows that continuous epidural morphine infusion, even in small doses, may cause peripheral edema in patients without a previous history of edema or venous stasis. Finally, we believe that some centrally mediated events involving both vasopressin release and urine composition alteration to be the underlying mechanism of peripheral edema associated with epidural morphine infusion.

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