CASE STUDY

Edema caused by continuous epidural hydromorphone infusion: A case report and review of the literature

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ABSTRACT

Background: *Intraspinal drug delivery (IDD) therapy has been increasingly employed in patients with intractable, nonmalignant pain. Before implantation of permanent intraspinal pump, an intraspinal opioid screening trial is conducted to demonstrate the efficacy. The patient-controlled continuous epidural opioid infusion trail, performed in an outpatient setting, is widely accepted by many interventional pain specialists.*

Objective: *To report a case of severe edema observed during the continuous epidural hydromorphone infusion trial.*

Case Report: *An otherwise healthy 68-year-old lady with a 5-year history of severe low back pain and bilateral leg pain because of failed back surgery syndrome was referred to our clinic for IDD therapy.*

A tunneled lumbar epidural catheter was placed at L2-L3 with catheter tip advanced to L1 under fluoroscopic guidance. Satisfactory catheter placement was confirmed by epidurogram. The catheter was then tunneled subcutaneously and connected to a Microject™ patient-controlled epidural analgesia (PCEA) pump (Codman, Raynham, MA). The pump was programmed to deliver hydromorphone (0.1 mg/ml) at basal rate of 0.3 ml/h. The bolus dose was 0.1 ml with a 60-minute lockout interval. The patient was instructed how to operate the infusion pump. During the following infusion trial, she reported satisfactory analgesia (>70 percent pain reduction) and was able to wean off her other systemic opioids. However, she developed diffuse edema and gained over 16 pounds during the 5-day infusion trial. Her edema finally resolved 3-4 days after termination of the epidural infusion.

Conclusion: *Edema may occur and persist during epidural hydromorphone infusion. This report represents the first case report, to the best of our knowledge, describing severe edema in a patient on continuous epidural hydromorphone administration during an outpatient epidural infusion trial.*

Key words: edema, epidural hydromorphone infusion, epidural morphine infusion, intraspinal drug delivery, failed back surgery syndrome

INTRODUCTION

Intraspinal drug delivery (IDD) pump therapy has been increasingly utilized in patients with intractable, nonmalignant pain.[1-5] It is well accepted that a temporary trial of intraspinal analgesic can be conducted, to document the effectiveness of analgesia, before the implantation of permanent intrathecal drug delivery pump.[1] 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 of 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 physicians to deliver selected analgesics mostly an opioid, for example, morphine or hydromorphone with or without local anesthetics, eg, bupivacaine, in a continuous fashion, with an on-demand bolus button accessible to the patient. Patients are discharged home to resume their usual activities of daily living. In our clinic, the outpatient infusion trial spans 1-2 weeks. The systemic opioids are usually weaned off during the trial. More than 50 percent pain reduction together with demonstrable improved functional level is considered a positive trial.[1]

CASE REPORT

An otherwise healthy, 68-year-old lady (5″4′, 131 lbs) was considered for IDD therapy. The patient had a 5-year history of severe low back pain and bilateral leg pain

because of the degenerative lumbar disc disease, lumbar spinal stenosis, and lumbar spondylosis. The patient underwent lumbar decompression and fusion at L4-L5 and L5-S1, after failing to respond to conventional treatments including medications, physical therapies, and spinal interventions.

The patient described her low back pain being equally bothersome to her bilateral leg pain. Her pain level was usually at 7-8/10 on numerical pain scale of 0-10. Her low back pain generally worsened by sitting, while her bilateral leg pain worsened by walking and standing. Her previous medical history was negative for any cardiac, hepatic, renal, vascular, or endocrine diseases. She did not have any previous history of venous stasis or leg edema. Her medications included fentanyl patch 50 mcg/h, hydrocodone/acetaminophen 10/500 qid prn, duloxetine 60 mg qhs, pregabalin 150 mg bid. Further dosage escalation of fentanyl patch caused persistent nausea and sleepiness. She had been on the aforementioned medications for over 3 months. Her lumbar MRI with and without contrast showed post-surgical changes of lumbar spine including paraspinal fixation rods from L4 through S1 and post-decompressive laminectomy at L4-L5 and L5-S1.

Following a preimplantation psychological evaluation confirming her candidacy, she underwent an outpatient patient-controlled continuous epidural hydromorphone trial. Hydromorphone infusion was decided instead of morphine because of the history of allergy to codeine.

A tunneled lumbar epidural catheter was placed at L2-L3 with catheter tip advanced to L1 under fluoroscopic guidance. Satisfactory catheter placement was confirmed by epidurogram and a test dose of lidocaine 20 mg. The proximal tip of the catheter was then tunneled subcutaneously and connected to a Microject™ PCEA pump (Codman, Raynham, MA) and reservoir bag containing preservative free hydromorphone 0.1 mg/ml. The pump was programmed to deliver at a basal rate of 0.3 ml/h. The bolus dose was 0.1 ml with a 60-minute lockout interval. The patient was instructed how to operate the infusion pump before discharging home. During the following 5-day infusion trial, she reported more than 70 percent reduction of her low back and leg pain. Her epidural hydromorphone infusion rate remained the same during the entire trial period. She only had to use the on-demand bolus doses averaging 3-4 times a day. She was able to wean off her oral and transdermal opioids completely. However, on Day 3, she started to notice swelling of bilateral lower extremities, initially in her feet, ankles. She was given the advice to keep her legs elevated whenever possible. However, over the following 2 days, the swelling became more diffuse, extending into her calves, knees, and thighs. By Day 5, the swelling extended further to abdominal and mid-thorax region. She gained over 16 lbs after being on the hydromorphone infusion for 5 days. She did not experience any other significant side effects besides edema and, her low back and leg pain improved significantly (>70 percent pain reduction). She insisted on discontinuing the infusion trial. Her edema finally resolved 3-4 days after termination of the epidural infusion, with the help of a few doses of furosemide (20 mg bid × 4 days).

DISCUSSION

Systemic opioids may cause peripheral edema.[9,10] Gardner-Nix reported five cases of peripheral edema due to systemic opioids in patients with nonmaligmant pain: two with transdermal fentanyl patch, two with morphine, and one with methadone.[9] Interestingly, of the two patients on oral morphine who developed edema, one did so when morphine dosage was slowly escalated to 400 mg every 8 hours, while the other one noticed pedal edema when morphine dosage was gradually up to 120 mg every 8 hours plus short-acting morphine 25 mg three timed daily as needed for "breakthrough pain." Before reaching the aforementioned dosage, there was no edema noted by the patients or physicians. Obviously, the daily morphine dosages in the mentioned cases, which precipitated leg edema, were quite large (435-1,200 mg/day). However, there has been no report in the literature, to the best of our knowledge, describing edema caused by systemic hydromorphone.

Multiple studies have shown that systemic morphine can cause histamine release,[11-14] which may, in turn, contribute to peripheral edema. Grossmann et al. 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 less or no roles in the process of venodilation.[13] This conclusion was compatible to what Gardner-Nix observed that edema tended to occur when oral morphine dosage was escalated to certain levels. Hydromorphone, a direct derivative of morphine, with similar pharmacokinetic and pharmacodynamic profiles to morphine,[15] has not been shown to cause histamine release. Guedes et al.[16] studied the effect of intravenous hydromorphone versus morphine administration on histamine release in dogs and concluded that intravenous hydromorphone induced histamine release only minimally, in contrast to intravenous morphine.

Our patient, however, received epidural hydromorphone infusion at 0.76 mg/day (conc.:0.1 mg/ml infused at 0.3 ml/h, avg. 4 boluses of 0.1 ml/day), during the 5-day epidural infusion trial and developed progressive edema. The minute hydromorphone dose infused epidurally in our patient, ie, 0.76 mg/day, which induced edema from Day 3, was in sharp contrast with her prior routine systemic opioids, ie, fentanyl patch 50 mcg/h (equivalent to 60-90 mg oral morphine)[17] plus hydrocodone 40 mg/day,

which did not cause any edema. Therefore, clearly, a centrally mediated mechanism is speculated.

Increased vasopressin release from posterior pituitary induced by opioid, a working hypothesis initially proposed by de Bodo[18] and subsequently by Bisset et al.,[19] was widely accepted to account for peripheral edema due to centrally administered opioid[20]; however, a few animal studies actually showed conflicting results in terms of vasopressin release to intraspinal morphine, that is, increased in some reports[21,22] whereas decreased in others.[23,24] However, there has been no report in the literature on edema due to epidural hydromorphone infusion. Indeed, most of the animal studies done investigated the vasopressin release following acute morphine administration up to 24 hours. To the best of our knowledge, the literature lacks such studies investigating the 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; however, this hypothesis needs further verification. Recall that our patient started to develop leg edema on Day 3 of the epidural hydromorphone infusion trial.

Nevertheless, some researchers believe that opioid-induced vasopressin release alone is an oversimplified view, and therefore inadequate to explain opioid-induced antidiuresis. Indeed, Huidobro-Toro and Huidobro first observed striking difference 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 very low concentration of urine electrolytes, suggesting opioids selectively activate central opioid receptors to produce changes in urine formation and composition.[25] This hypothesis was further substantiated by Danesh and Walker through their demonstration that centrally administration of morphine in conscious rats enhanced renal tubular sodium reabsorption, the antinatriuretic effect, by an opiate receptor-dependent mechanism.[26] 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; however, the exact mechanism needs further characterization. The opioid receptor involved, based on evidence so far, pointed to mu-type response.[26]

It is noteworthy that our patient, obviously with opioid tolerance, did not develop any peripheral edema while on systemic opioid. This could not be explained from either the histamine release mechanism[13] or centrally mediated renal modulating mechanism of systemic opioids[26] as proposed by Danesh and Walker. We speculate that there could be some type of threshold points or dosage above which events mediated through the aforementioned mechanisms would occur.

Peripheral edema has also been increasingly recognized as a problematic side effect with chronic intrathecal opioid infusion therapy.[20,27-30] Aldrete and Couto da Silva reported five cases of leg edema in 23 patients on long-term intrathecal opioids (three on oxymorphone 6-13 mg/day and two 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 concluded that "Pre-existing led venous insufficiency and edema may be relative contraindications for the continued use of intrathecal opioids in patients with chronic pain".[27] Anderson et al. reported, in their retrospective study of 37 patients on long-term intrathecal opioid therapy, that 16 percent of the patients developed problematic leg edema while on intrathecal morphine infusion. Switching to intrathecal hydromorphone only transiently improved the leg edema.[28]

There was no discussion in the report whether any of the patients, who developed leg edema on intrathecal infusion, had pre-existing edema or venous stasis. The authors also seemed to believe the interaction of opioid with pituitary, leading to the release of vasopressin from posterior pituitary, to be the underlying mechanism.[20]

It is puzzling, yet fortunate that only a small percentage of patients (6.1-21.7 percent) on intrathecal opioid therapy, who developed leg edema,[27-29] with the highest percentage (21.7 percent) being reported in patients having pre-existing leg edema or venous stasis.[27] It seems reasonable to believe what Aldrete and Couto da Silva suggested that the pre-exiting conditions such as edema and/or venous stasis predisposed patients to the development of leg edema[27]; however, the exact mechanism may not be what they speculated as opioid dose-dependent vasodilation. Studies, in patients without any of the aforementioned pre-existing conditions, yet with the development of edema, are needed 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 hydromorphone infusion instead of intrathecal infusion. There have been no previous reports in humans or animals, to the best of our knowledge, describing the development of edema while on continuous epidural hydromorphone infusion let alone in the setting of outpatient epidural infusion trial.

Recently, we submitted a case report of severe peripheral edema during an outpatient continuous epidural morphine infusion trial in a patient with failed back surgery syndromes (accepted for publication). Although there are similarities between these two cases, ie, both patients were otherwise healthy without previous histories of hepatic, renal, cardiac, endocrine, vascular diseases, or venous stasis/leg edema, both received continuous epidural opioid infusion in minute doses in comparison

with their prior systemic opioids; the difference lies in the infused opioid, ie, hydromorphone in this case while morphine in the other.

We believe that the edema, associated with epidural or intrathecal opioid infusion, whether it is hydromorphone or morphine, shares similar mechanism, which probably involves centrally mediated events including both vasopressin release and urine composition alteration. Long-term prospective studies that compare urine and serum electrolytes in patient pre- and post-pump implantation as well as serum vasopressin level follow-up may help to clarify the underlying mechanism of this complication.

We further believe that it may be worthwhile to 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 be dealing with this complication a lot more often because of increasing popularity of IDD therapies for both malignant and non-malignant pain.

CONCLUSION

This case report shows that continuous epidural hydromorphone infusion, even in very small dose, may cause edema in patient without previous history of edema or venous stasis. We further believe that some centrally mediated events involving both vasopressin release and urine composition alteration to be the underlying mechanism of edema associated with epidural hydromorphone infusion.

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