CLINICAL REPORT

Intentional Intrathecal Opioid Detoxification in 3 Patients: Characterization of the Intrathecal Opioid Withdrawal Syndrome

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■ **Abstract**

Objective: Intrathecal (IT) drug delivery systems for patients with chronic non-malignant pain are intended to improve pain and quality of life and reduce side effects of systemic use. A subset of patients may have escalating pain, functional decline, and/or intolerable side effects even as IT opioid doses are increased. Discontinuation of IT medications may represent a viable treatment option but strategies to accomplish this are needed.

Subjects and Interventions: Three patients with intrathecal drug delivery systems (IDDS), inadequate pain control, and declining functionality underwent abrupt IT opioid cessation. This was accomplished through a standardized protocol with symptom-triggered administration of clonidine and buprenorphine, monitored using the clinical opiate withdrawal scale.

Results: Symptoms of IT withdrawal were similar in all patients and included diuresis, agitation, hyperalgesia, mild diarrhea, yawning, and taste and smell aversion. Hypertension and tachycardia were effectively controlled by clonidine administration. Classic symptoms of withdrawal, such as piloerection, chills, severe diarrhea, nausea, vomiting, diaphoresis, myoclonus, and mydriasis, were not noted. At 2 to 3 months follow-up, patients reported decreased, but ongoing pain, with improvements in functional capacity and quality of life.

Conclusions: This preliminary work demonstrates the safety of abrupt IT opioid cessation utilizing standardized inpatient withdrawal protocols. To our knowledge, these are among the first reported cases of intentional, controlled IT opioid cessation without initiation of an opioid bridge: self-reported pain scores, functional capacity, and quality of life improved. The IT opioid withdrawal syndrome is characterized based upon our observations and a review of the literature. ■

Key Words: opioids, infusion pumps, implantable, detoxification

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Jackson and Lonergan contributed equally to this work as first authors.

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INTRODUCTION

The long-term effectiveness of opioid administration in patients suffering from chronic non-malignant pain has not been established.[1–5] Nevertheless, when patients

with non-malignant pain are unable to tolerate large doses of systemic opioids secondary to adverse side effects, or have pain refractory to routine management, an alternate route for opioid administration using an intrathecal drug delivery system (IDDS) is frequently employed as the next step in pain management. As with systemic opioids, data to support long-term intrathecal (IT) opioid administration in patients with chronic non-malignant pain remains controversial. This is confounded by the fact that many of these patients are co-administered oral and IT opioids, and multiple off-label combinations of IT medications are typically used without the requisite evaluation in human clinical trials.[6–10] Of concern, Coffey has recently described higher early and late mortality rates after initiation of IT therapy compared to similar patients with non-cancer pain undergoing alternative pain management.[11] Strategies have been employed to address the complications associated with IDDS, such as drug rotation and the utilization of non-opioid formulations. Grider et al.[12,13] describe a method of IDDS initiation that includes tapering of systemic opioids followed by ultra-low doses of IT morphine, with promising initial results.

Adverse effects and outcomes related to IT therapy are related either to the infused medication or the device itself. Side effects of IT medications vary depending on the medication used, but common opioid-related side effects include nausea, vomiting, excessive sweating, weight gain, peripheral edema, urinary retention, pruritus, and sexual dysfunction. Device-related complications include granuloma formation, catheter fracture or migration, CSF leak, infection, seroma, hardware erosion, and pain at the pump site.[6,14,15] Drug abuse is less of an issue with IT opioids than with oral medications, but self-extraction of concentrated IT medications for IM or IV use has been described in the literature.[16,17]

Patients have been reported to have a loss of pain control and/or an increase in pain perception after a period of time on IT opioid therapy at rates of up to 20% to 30%.[6,14] Hyperalgesia induced by opioids is well-described for systemic opioid administration in both chronic pain patients and addicts.[18–20] Multiple case reports describe improvement of pain with a decrement in systemic opioid dosing.[21,22] A retrospective study at Vanderbilt described 23 patients who had undergone high-dose systemic opioid detoxification and found that 91% of patients reported a significant decrease in pain after detoxification.[23] Analogous information related to discontinuation of IT opioid treatment has not been reported in the literature.

The association between opioid dependence, tolerance, withdrawal, and opioid-induced hyperalgesia (OIH) has been the subject of intense investigation in recent years, and the clinical picture can often be confusing. When a patient experiences a loss of analgesia or functionality during chronic IT opioid therapy, tolerance, disease progression, or OIH may all manifest clinically as a higher dose threshold for analgesic effect. Tolerance or disease progression should respond to dose increase with analgesia or increased functionality; OIH may worsen with dose escalation, along with a concomitant decline in functionality. Multiple review articles exploring the postulated mechanisms of OIH in humans have been published in recent years.[20,24–27]

Based on the weight of this evidence, opioid detoxification is often recommended when patients demonstrate multiple adverse effects, or a lack of improvement in function or quality of life after chronic opioid use. Opioid detoxification is a commonly used, albeit potentially misleading, term used in the literature to describe planned cessation of opioid therapy; use of the term detoxification is employed here for consistency, but does not imply the presence of addiction. Although many patients may be concerned that discontinuing opioid therapy will result in an increased level of pain, it is not uncommon that reported pain levels are unchanged or improved following detoxification. Furthermore, gains in functionality and loss of adverse side effects are also commonly observed. Detoxification from systemic opioids can typically be safely and reliably accomplished on both inpatient and outpatient bases.

When patients with previously implanted IDDS in whom pain persists, worsens, or is associated with functional decline or intolerable side effects, an algorithm of medication rotation has been the standard of care. The option of detoxification has traditionally been reserved for cases of pump malfunction and has typically been carried out with intravenous or IT bridging using similar medications. Often, dose escalation and addition of IT adjuncts has already been employed by the time the patient is evaluated at a tertiary referral center. Very little has been published about the management of these exceedingly complex patients once the customary treatment options have been exhausted. We report here 3 cases in which intentional, controlled IT opioid cessation without initiation of an opioid bridge was elected as appropriate

treatment and describe for the first time the characteristics of the associated syndrome of IT opioid withdrawal.

METHODS

Three patients with unsatisfactory results from IDDS were evaluated in our clinic in late 2010 and early 2011, and a trial of detoxification from IT medications was recommended. Scant clinical literature could be found describing the IT opioid withdrawal syndrome, or if this could be managed without the administration of oral or intravenous opioid replacement and its subsequent cessation. Inpatient detoxification was therefore planned in the Neuro-Intensive Care Unit for careful monitoring during implementation of a standard detoxification protocol routinely employed in the Vanderbilt Addiction Center.

Informed consent was obtained from each patient, including a discussion about the unpredictability of IT withdrawal symptoms. Any life-threatening, unexpected side effects would result in an immediate administration of IV opioids or resumption of IT opioids via the existing pump, as has been described safely and effectively in cases of pump malfunction.[8,27–31] The patients expressed understanding and voluntarily agreed to a trial of detoxification.

An 11-item clinical opiate withdrawal scale (COWS) was used to rate withdrawal severity.[32] Administration of oral clonidine was triggered by COWS scores > 5. Intramuscular buprenorphine was to be initiated only when COWS scores rose to 15, in order to diminish the possibility of precipitated opioid withdrawal. This protocol was designed for detoxification of addicts, but has also been successfully employed in chronic pain patients desiring detoxification from high-dose opioid therapy.

All primary treating physicians were consulted prior to detoxification to ensure maximization of care for any chronic medical conditions; we also proceeded with our own risk assessment as if the physiological stresses of withdrawal were akin to a general anesthetic, and did ''preoperative'' evaluations accordingly.

RESULTS

Case 1

A 52-year-old man with a long history of post-laminectomy lumbar and bilateral leg pain, neurogenic claudication, obesity, obstructive sleep apnea, depression, peripheral vascular disease, and diabetes presented for evaluation. His lumbar pain began in 1993 and had progressed over an 8-year period, during which time he underwent L4-5 fusion, spinal cord stimulator placement (2004) and IDDS implantation (2006). Despite transition from IT morphine to IT hydromorphone, and subsequent dose escalation of hydromorphone from 0.5 to 2.45 mg/day over 1 year, his pain worsened and became more generalized. He also reported over-sedation, depression with anhedonia, sexual dysfunction, lower extremity edema, weight gain and declining functionality corresponding with escalation in IT opioid therapy. His pre-admission average pain score was 7/10.

Admission vital signs were as follows: blood pressure 164/55, pulse 57, respiratory rate 17, oxygen saturation 92%, and weight 172.4 kg. The IDDS was turned off and the COWS protocol initiated. Vascular claudication was ruled out with a normal ankle-brachial index in combination with normal imaging studies of a previous aorto-iliac bypass graft.

Withdrawal began with a dramatic diuresis about 12 hours after discontinuation of the IT hydromorphone. This progressed to mild dysphoria, taste and smell aversion with loss of appetite, intermittent nausea and mild diarrhea. Several hypertensive episodes were observed, which were effectively treated with oral clonidine according to the protocol. During withdrawal, he required a maximum of 0.6 mg clonidine/24-hour period, with a maximum COWS score of only 9; therefore, he did not meet the minimum criteria required for buprenorphine initiation (Figure 1). He did have 1 episode of chest palpitation with chest pain associated with monitored PVCs and otherwise normal vital signs. An EKG showed non-specific T wave abnormalities. Magnesium was administered with complete resolution of his symptoms. The cardiology service was consulted and monitored him throughout the duration of his hospital stay. A surface echocardiogram showed no wall motion abnormalities and cardiac enzymes were normal. The psychiatry service also followed the patient throughout his hospitalization to monitor his depression and assist in the withdrawal protocol.

Approximately 4 days after IT medication discontinuation, his appetite returned, his agitation improved, and he was able to get out of bed with improved mobility. Upon discharge from hospital on day 6, his pain score was rated a 1/10 with a significant reduction in

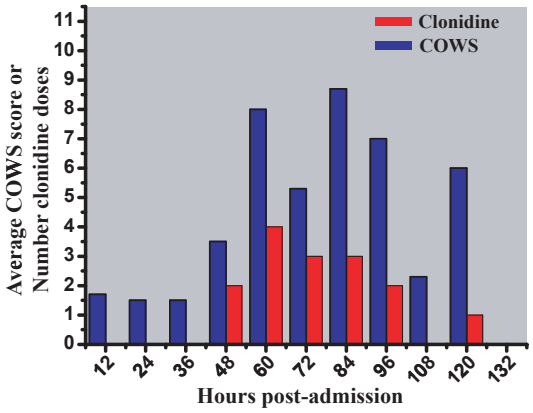

Figure 1. Clinical opiate withdrawal scale (COWS) scores and total number of oral clonidine doses (0.1 mg)/12-hour period for case 1 during admission in the ICU. The COWS scores peaked at 84 hours and the clonidine administration peaked at 60 hours.

pain while walking. His lower extremity edema had completely resolved. He had lost 12.6 kg with a discharge body weight of 159.8 kg. His IDDS was filled with saline and programed to run at a minimal rate; he was discharged with acetaminophen for pain and a prescription for daily physical therapy, exercise, and instructions for better health maintenance.

At a routine 2-month follow-up, he reported his average pain score as 6/10. He did report subjective improvement in functionality and decreased somnolence. He was participating in physical therapy, and although it was difficult, this had not been possible prior to detoxification because of somnolence and fatigue. He expressed continued frustration and discouragement with persistent back pain exacerbated by activity, although his leg pain and lower extremity edema had not returned. There was no appreciable improvement in blood glucose control or continued weight loss (weight 163.5 kg), although symptoms of anhedonia had improved with the patient reporting improvement in taste sensation and again finding pleasure in spending time with family. He had continued to remain off of opioid therapy at 1 year and has relied on meloxicam 15 mg daily, amitriptyline 50 mg nightly and over-the-counter analgesics for pain control.

Case 2

A 68-year-old woman with post-laminectomy lumbar pain, hypertension, cerebrovascular disease, and diabetes presented for evaluation. In the 1990's, the patient had 7 lumbar spine surgeries, the most recent in 1999. In 2002, she underwent implantation of a spinal cord stimulator. Although this helped initially, her pain progressed and oral methadone and hydromorphone were initiated and escalated. With dose escalation, the patient began to have intolerable side effects and an IDDS was placed in December of 2008. IT medications trialed had included morphine, hydromorphone, and bupivacaine. Opioid rotation and escalation only seemed to result in continued progression of her pain, decreasing functionality and worsening lower extremity edema. At the time of initial evaluation, she was receiving 2.2 mg/day of both IT hydromorphone and bupivacaine, as well as 20 mg oral methadone daily. Her pain was an average intensity of 9/10.

Four days prior to admission, she discontinued the oral methadone. Admission vital signs were as follows: blood pressure 139/73, pulse 84, respiratory rate 13, oxygen saturation 96%, and weight 90.5 kg. The IDDS was turned off and the COWS protocol initiated. She was treated primarily with oral clonidine and never attained a score high enough to require IM buprenorphine. She required a maximum total dose of 0.9 mg clonidine/24-hour period, with a maximum COWS score of 11 (Figure 2).

Her symptoms of withdrawal began with increasing joint pain and diuresis approximately 12 hours after pump discontinuation. Throughout the withdrawal period she also demonstrated agitation, nausea, mild diarrhea, and anxiety. She remained hypertensive (140s to 190s SBP) despite clonidine administration. She reported significant taste and smell aversion with loss of appetite. The symptoms of withdrawal gradually improved 4 to 5 days after IDDS discontinuation. Sublingual buprenorphine was initiated after detoxification for analgesic purposes. She was discharged with a pain score of 7/10 (improved by 2 points since admission), heightened alertness and mild nausea (which was thought to be related to buprenorphine therapy). Similar to the first case, her lower extremity edema had completely resolved. Her weight on the day of discharge was 84.7 kg, which represented a 5.8 kg loss. Her IDDS was filled with saline and programed at a minimal rate.

At routine 2-month follow-up, she endorsed continued frustration with pain (average intensity of 7/10) but with a dramatic improvement in functional capability, quality of life, and mental clarity. Her weight was 85.9 kg, with continued resolution of lower extremity edema. She was maintained with 8 mg sublingual buprenorphine twice daily and 100 mg amitriptyline

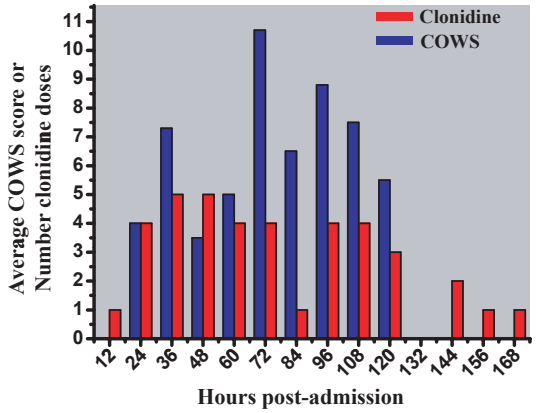

Figure 2. Clinical opiate withdrawal scale (COWS) scores and total number of oral clonidine doses (0.1 mg)/12-hour period for case 2 during admission in the ICU. The COWS scores peaked at 72 hours and the clonidine administration peaked at 36 to 48 hours.

nightly. At 1 year, the patient continued to report 7/10 pain, but she and her family readily endorsed that her quality of life had been much improved.

Case 3

An 80-year-old woman with a long history of lumbar pain, hypertension, and osteoarthritis presented for evaluation. She had undergone 3 lumbar surgeries and eventually had an IDDS placed at an outside center 9 years prior. She reported that over the past year, the IDDS was not providing consistent or adequate analgesia despite upward titration from 0.37 to 0.76 mg of hydromorphone/day. She was also receiving 3 mg/day of IT bupivacaine and intermittent oral hydromorphone (4 mg every 4 hours as needed). The increase in IT and oral hydromorphone dosage corresponded with a decline in function and difficulty performing activities of daily living. She complained of an average of 5/10 pain in her low back and lateral thighs. On physical exam, lower extremity edema was not noted (in contrast with cases 1 and 2). The decision was made to proceed with inpatient detoxification in a monitored hospital ward, rather than the ICU, given the mild withdrawal symptoms observed with the first 2 cases.

Admission vital signs were as follows: blood pressure 195/78 (which improved following clonidine administration), pulse 64, respiratory rate 18, oxygen saturation 96%, and weight 72.6 kg. Her last dose of oral hydromorphone was 10 hours prior to admission. Within 24 hours of cessation of the IDDS, she started experiencing symptoms of withdrawal, which included severe pain in her back and legs, hypertension (effectively treated with clonidine), diuresis, yawning, frequent sneezing, restlessness, lacrimation, and agitation. She was treated with oral clonidine according to the COWS protocol, with the maximum score of 8 and maximum total dose of 0.8 mg of clonidine/24-hour period (Figure 3). She was also treated with gabapentin and acetaminophen. She did not receive any opioids, and the withdrawal symptoms were not severe enough to qualify for buprenorphine administration. Symptoms of withdrawal had subsided by the fourth hospital day. She was discharged on the 5th day with a pain score of 4/10 and reported much less pain in her legs while walking, which she associated with the clonidine doses. In contrast with the first 2 cases, she did not experience significant weight loss throughout her hospital stay. The IDDS was filled with saline and programed at a minimal rate.

At routine 3-month follow-up, the patient reported that she was doing extremely well with a baseline pain score of 2/10. She was able to perform all activities of daily living and was walking 1 mile daily. She also reported better control of her hypertension since detoxification. She was maintained with clonidine 0.1 mg twice daily, gabapentin 600 mg 3 times daily, and acetaminophen as needed. At 1 year, the patient reported that her activities are no longer limited by pain.

DISCUSSION

The Treatment of Withdrawal: Clonidine and Buprenorphine

Knowledge of the pathophysiology of systemic and IT opioid withdrawal is still evolving, and to our knowledge, these are among the first reported cases of intentional-controlled IT opioid cessation without initiation of an opioid bridge.[16] Systemic opioid withdrawal is manifested by a constellation of symptoms including nausea, vomiting, diarrhea, abdominal cramping, tremor, piloerection, mydriasis, diaphoresis, craving, anxiety, rhinorrhea, sleep disturbance, temperature dysregulation (chills and fever), hyperalgesia, anorexia, and hyperpnea. These systemic symptoms have long been shown to be ameliorated by oral administration of opioids as well as clonidine.[33,34]

Clonidine is a centrally acting α-2 adrenergic agonist that reduces the symptoms of sympathetic activation related to opiate withdrawal. The efficacy of clonidine is thought to be due to reduced activity of

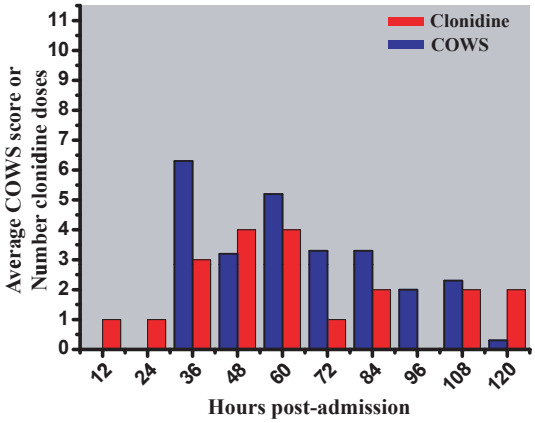

Figure 3. Clinical opiate withdrawal scale (COWS) scores and total number of oral clonidine doses (0.1 mg)/12-hour period for case 3 during admission in the monitored ward. The COWS scores peaked at 36 hours and the clonidine administration peaked at 48 to 60 hours.

noradrenergic locus coeruleus (LC) neurons, with subsequent suppression of the autonomic signs of withdrawal.[35] Some of the subjective effects of opiate withdrawal such as abdominal cramps and bone pain are not reliably reduced by administration of clonidine.[36,37] The use of clonidine is limited by accompanying side effects that include hypotension, dizziness, dry mouth, and sedation.[38]

The partial mu-opioid agonist buprenorphine has also been extensively utilized in opioid detoxification and is now the mainstay of treatment of opioid withdrawal as intensity of withdrawal symptoms increase. Buprenorphine has a favorable side-effect profile for ameliorating symptoms of withdrawal, and a Cochrane review reports that it is superior to clonidine and lofexidine in terms of symptom resolution, tolerability, and facilitation of treatment completion.[39]

When contemplating the use of buprenorphine for the treatment of withdrawal, the clinician must be aware that administration of buprenorphine in persons physically dependent on full-agonist opioids may trigger an extremely intense precipitated withdrawal syndrome. This has been described extensively in the addiction literature.[40–42] Therefore, in any detoxification protocol, buprenorphine should not be administered before scores indicating significant withdrawal have been reached. No data regarding administration of systemic buprenorphine to patients dependent on IT opioids was available at the time of this report. It is relevant to note that multiple recent European trials of transdermal buprenorphine for analgesia have not demonstrated any adverse side effects or lack of efficacy from using morphine as a rescue medication in patients maintained on a buprenorphine transdermal patch, nor did opioid rotation from transdermal fentanyl to transdermal buprenorphine cause precipitated withdrawal.[43–45]

IT Opioid Withdrawal: Characterization and Mechanisms

In humans, there are only a few case reports in the literature that describe IT withdrawal symptoms reported after pump malfunction or failure. The only case report describing abrupt IT opioid cessation without an opioid bridge involved an addict who was diverting opioids from the IDDS reservoir.[17] This patient also had a catheter granuloma requiring IDDS removal and detoxification using only a clonidine patch. However, it is not clear whether this patient was also using oral opioids or other illicit substances, or the dose of IT medication at the time of IDDS explantation. The withdrawal syndrome was not described. Another patient experienced fever, leukocytosis, impaired sense of smell, allodynia, and hyperpathia in the limbs after abrupt cessation of a 3-week IT opioid trial.[46] Another described "pain, jitters, and an inability to function," not further described in detail, after the IT catheter separated from the reservoir containing morphine and bupivacaine.[29] Another patient had symptoms of agitation, hyperthermia, hypertension, vomiting, tachycardia, and pain after receiving a single IT bolus of morphine after cessation of oral opioids for 15 hours, which were most likely related to systemic rather than IT withdrawal, and resolved with IV morphine.[30] Rafaelli et al. described a case series of IT opioid detoxification for patients with poor functionality. However, because withdrawal was bridged with IV morphine, oral clonidine, ketoprofen, and lorazepam for 3 days, followed by tramadol, clonidine, and ketoprofen for 10 days prior to transition to ziconotide intrathecally, the withdrawal syndrome from IT opioids could not be characterized.[47]

Consistent withdrawal symptoms in all 3 of our patients suggest that we have identified some fundamental aspects of IT opioid withdrawal in this small case series (Table 1). These signs and symptoms included marked hypertension, restlessness, myalgias, yawning, dysphoria, profound taste and smell aversion, diuresis (in the 2 of 3 patients with preexisting lower extremity edema), and hyperalgesia. In rats, symptoms of spinal withdrawal—hyperalgesia, HTN, and body weight loss—are similar to responses seen in withdrawal from systemic opioids, although some

responses like hyperthermia, teeth chattering, and behavioral manifestations like jumping were not.[48] Our patients, likewise, did not exhibit many of the symptoms of classic systemic opioid withdrawal, such as mydriasis and piloerection, but experienced symptoms consistent with animal models of spinal withdrawal. Specific signs and symptoms of IT opioid withdrawal and differences between IT and systemic withdrawal syndromes will be discussed later, with available published data to support our observations.

Hyperalgesia

Hyperalgesia throughout the opioid withdrawal period is an almost ubiquitous phenomenon and may have shared mechanisms with OIH that manifests during opioid therapy. In the reviewed literature, the term "OIH," is used both when describing hyperalgesia secondary to withdrawal and that involving OIH secondary to acute or chronic opioid administration. The fundamental mechanisms of OIH are likely similar in both settings, but there may be clinical and experimental situations (nerve injury, for example) in which modulation of these mechanisms may occur. This may explain the observation that withdrawal-induced hyperalgesia appears to be virtually ubiquitous in the clinical setting, but OIH secondary to acute or chronic opioid administration is not. In either case, hyperalgesia is thought to involve NMDA-facilitated central sensitization and increase in spinal pronociceptive neurotransmitters like substance P (SP) and calcitonin gene-related peptide (cGRP).[25] Excitatory substances in the descending rostral ventromedial medulla (RVM) that lead to enhanced nociception have also been described.[49,50] In particular, cholecystokinin release via colocalized cholecystokinin and mu-opioid receptors in RVM neurons appear to be involved in descending facilitation of neuropathic pain and hyperalgesia.[25,51–54]

Table 1. Based Upon Our Clinical Observations and a Review of the Literature, a Comparison of Symptoms Between Systemic and Intrathecal (IT) Opioid Withdrawal[32,33]

Withdrawal Symptoms	Systemic	Intrathecal*
Tachycardia	Yes	Mild
Hypertension	Yes	Yes
Diaphoresis	Yes	No
Restlessness	Yes	Yes
Mydriasis	Yes	No
Arthralgias/Myalgias	Yes	Yes
Rhinorrhea	Yes	Mild
G.I. Upset	Yes	Mild
Tremor	Yes	Mild
Yawning	Yes	Yes
Dysphoria	Yes	Yes
Piloerection	Yes	No
Taste/smell aversion	Yes	Yes
Diuresis	?	Yes
Hyperalgesia	Yes	Yes
Hyperpnea	Yes	?
Temp dysregulation	Yes	?

*Intrathecal withdrawal symptoms possibly masked by clonidine administration.

There are also other, non-opioid, mechanisms purported to be involved in the pronociceptive aspects of withdrawal.[18] For example, noradrenergic and cholinergic pathways have been implicated in analgesia. Clonidine and other α-2 agonists are thought to have a primarily spinal site of action, as spinal cord transection does not affect the analgesia.[55] Analgesia from α-2 agonists in the spinal cord is mediated in part by the activation of inhibitory G proteins that reduce the release of pronociceptive substance P and glutamate. α-2 agonists also stimulate both antinociceptive acetylcholine release and the upregulation of muscarinic Ach receptors; as these are upregulated after nerve injury, their activation is useful for amelioration of neuropathic pain.[56] Clinically, hyperalgesia induced by systemic opioid withdrawal is also significantly improved by IT clonidine,[57] which may be related to alterations in catecholamine metabolism.[58] Eisenach et al.[55] reported that IT, but not intravenous, clonidine could reduce experimental pain and hyperalgesia in humans. As we used oral clonidine in our withdrawal protocol, it is unclear how much this contributed in attenuating the hyperalgesia of withdrawal.

Although none of our patients met clinical criteria for buprenorphine administration during IT opioid withdrawal, buprenorphine can be used to manage the hyperalgesia of systemic withdrawal. Recent data in rats suggest that this effect may be dose-dependent and that buprenorphine may induce hyperalgesia at ultralow doses.[59–61] The doses administered according to the COWS protocol are consistent with those described as antinociceptive and antihyperalgesic. The implied assumption is that our 3 patients, having undergone escalation of IT opioid dosing without improvement in analgesia or functionality, had OIH from 1 or a combination of the mechanisms described earlier. Self-reported improvements in pain after detoxification may be related to a rapid resolution of OIH, but also may be secondary to other factors, including placebo effect, buprenorphine effect in the 1 patient receiving it, enhanced effect of non-opioid medications such as gabapentin and amitriptyline, an analgesic

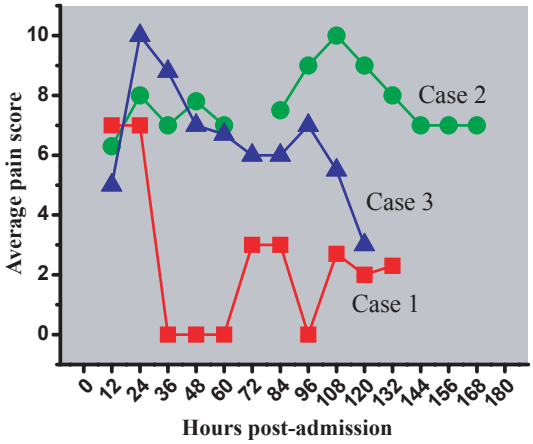

Figure 4. Average pain scores for cases 1, 2, and 3 during hospital admission. Case 1 reported improved pain scores within 36 hours of IT opioid discontinuation.

effect of oral clonidine, or an improvement in other factors as discussed later. Given the antinociceptive and antihyperalgesic medication profile of buprenorphine, it may be reasonable to continue this medication after the withdrawal period in those who continue to suffer from severe pain, or as first line monotherapy in those who have recrudescence of pain.

Multiple mechanisms resulting in hyperalgesia have been proposed and are discussed in detail in other reviews.[19,20,26,62,63] In all 3 patients, symptoms consistent with OIH were observed prior to detoxification and at various stages throughout the withdrawal period (Figure 4), although case 1 surprisingly reported resolution of hyperalgesia within 36 hours after IT opioid discontinuation. The clonidine and buprenorphine used to treat withdrawal symptoms may have antinociceptive and antihyperalgesic effects.

Hypertension

Clonidine appeared to blunt the autonomic response to withdrawal in our patients (Figure 5); however, it is unclear whether this is a peripheral, spinal, or supraspinal effect. Withdrawal from spinal opioids, experimentally induced by naloxone, will typically induce a pressor response in rats.[48] Supraspinal sites may mediate a more intense pressor response to naloxone than caudal sites, while other cardiovascular and behavioral signs of withdrawal are mediated exclusively via spinal cord pathways.[64,65] This redundancy may allow for different medications to ameliorate different signs and symptoms of withdrawal. Buccafusco described clonidine as effective for the central autonomic, but not

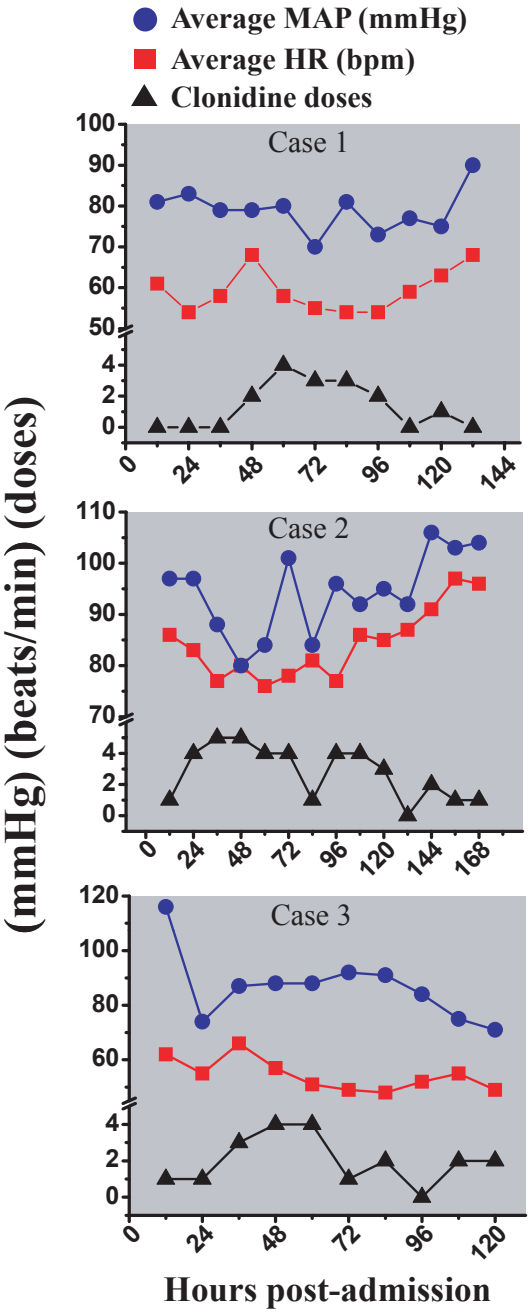

Figure 5. Average mean arterial pressure (MAP), average heart rate (HR), and total 12-hour clonidine doses during withdrawal. The administration of clonidine effectively blunted the sympathetic response.

behavioral, effects of withdrawal in rats. This may explain amelioration of HTN in our patients through the use of clonidine, without any significant reduction of anxiety, irritability, or other behavioral manifestations of withdrawal.

Although the mechanism is unclear, cholinergic stimulation at the level of the spinal cord typically

augments sympathetic activity and results in hypertension. Anticholinergic administration to rats experiencing opioid withdrawal results in a blunting of autonomic pressor response; however, this requires an intact spinal cord, suggesting a descending spinal cholinergic pathway that facilitates the autonomic response to IT opioid withdrawal.[66,67] This cholinergic excitatory descending pathway activates sympathoexcitatory preganglionic synapses in the case of an intact spinal cord, and IT clonidine reduces post-withdrawal increases in MAP via interaction with cholinergic neurons. This could not be explained by redistribution of the drug from spinal to rostral sites.[57] In fact, there is an intrinsic inhibitory cholinergic system that functions reflexively at the level of the spine to reduce CV outflow.[65,67–70] Therefore, although complex and incompletely understood, the autonomic cholinergic inhibitory system is thought to be spinal, while the facilitatory system is more supraspinal. Clonidine, via interaction with anticholinergic pathways, probably acts at the level of the spinal cord to preferentially inhibit the descending autonomic excitatory systems.

Diuresis and Resolution of Lower Extremity Edema

Two of 3 patients developed lower extremity edema while on IT opioid therapy (cases 1 and 2). Multiple authors have previously reported lower extremity edema in patients maintained on IT opioids, at rates ranging from 6% to 21%.[14,71–73] One case report also describes resolution of recurrent cellulitis in the setting of IT opioids and peripheral edema after transition from opioids to IT baclofen and clonidine.[74] It has been postulated from data in rats that the lower extremity edema is secondary to both a centrally mediated renal effect resulting in alterations in renal electrolytes, and/or a centrally mediated release of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH).[75–77] In both patients with lower extremity edema, a dramatic diuresis at the onset of withdrawal correlated with edema resolution (Figure 6). This significantly enhanced the ability in each to mobilize and ambulate with less pain.

Decrease in Body Weight

Decrease in body weight is observed during IT opioid withdrawal in the rat, thought to be secondary to a combination of diuresis, diarrhea, and possible food aversion.[48,78] None of our cases exhibited significant diarrhea, and all had profound taste aversion, but only the 2 patients with diuresis exhibited significant weight loss during detoxification.

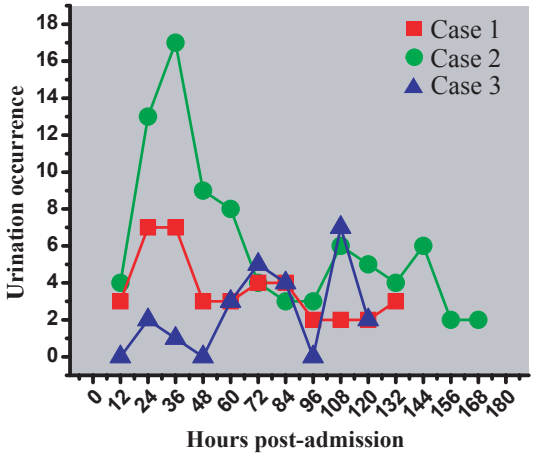

Figure 6. Incidence of urination per 12 hours period for each patient during hospitalization. Cases 1 and 2 had a profound diuresis that began 12 to 24 hours after admission, with corresponding resolution of LE edema.

Behavioral and Aversive Symptoms

Controversy exists regarding the involvement of the LC in the behavioral aspects of withdrawal. Several reports have described a noradrenergic hypothesis of opioid withdrawal originating in the LC.[33,79–82] Others contend that the autonomic and somatic components of withdrawal are localized to neurons in the periaqueductal gray, anatomically quite close to the LC.[83,84] Recently, the activation of ventral tegmental area (VTA), the origin of the mesolimbic dopamine system responsible for reward, has also been noted to induce anxiety in rats undergoing acute opioid withdrawal.[85] Opioids activate reward circuits by disinhibiting dopaminergic neurons in the VTA, which project to the nucleus accumbens and amygdala, areas of known emotionality, motivation, and impulsivity. These behavioral components, including anxiety and irritability, were seen in our patients and may be mediated by similar pathways.

The nucleus accumbens (NA) has also been implicated in the development of a conditioned taste aversion associated with opioid withdrawal. Injection of an opioid antagonist in the nucleus accumbens of a morphine-dependent rat has been shown to lower dopamine levels and result in the release of acetylcholine, which is postulated to contribute to the aversive sensory state of withdrawal.[86]

Lack of Significant GI Side Effects

Two of our patients discontinued oral opioid therapy prior to admission for IT detoxification. One patient discontinued hydromorphone (4 mg prn) 10 hours prior to admission; the half-life of oral hydromorphone is reported to be around 2.5 hours, so much of this was likely to have undergone elimination prior to the onset of IT withdrawal symptoms.[87] The patient maintained on 20 mg of methadone until 4 days prior to admission may have had some overlap between IT and systemic withdrawal syndromes, given the variable terminal elimination half-life of 33 to 46 hours for methadone.[88]

Rhode et al. studied the stigmata of different sites of withdrawal in the sacral spinal cord of rats. Selective peripheral withdrawal, with an antagonist that does not cross the blood–brain barrier (BBB), induced diarrhea without other systemic signs. Selective IT withdrawal with an antagonist that did not cross the BBB did not provoke diarrhea.[89,90] This peripheral selectivity may be why the GI side effects of systemic withdrawal were not seen to any significant degree in our patients. Patients on adjuvant oral opioid therapy may be more likely to manifest GI side effects compared with those on IT opioids alone, which is generally supported by our clinical observations.

CONCLUSIONS

This is the first description of intentional IT opioid withdrawal managed with a standardized COWS protocol utilizing oral clonidine and IM buprenorphine. As an opioid bridge was not utilized, the characteristics and full duration of IT opioid withdrawal could be observed and characterized. The symptoms showed some similarity across 3 patients and consistency with the existing human and animal literature to date. The symptom constellation was distinct from the systemic opioid withdrawal syndrome, and primarily involved hyperalgesia, hypertension, diuresis with resolution of lower extremity edema, smell and taste aversion, anxiety, and irritability. GI and other peripheral side effects, which are prominent in systemic opioid withdrawal, were mild or absent.

The safe and effective amelioration of the majority of IT withdrawal symptoms with oral clonidine monotherapy is potentially of great clinical import and has not previously been described in the literature. In the treatment of systemic dependence, clonidine alone is typically insufficient and requires augmentation with buprenorphine or an opioid agonist. It is possible that peripheral manifestations are minimal in IT withdrawal and that clonidine effectively attenuates central symptomatology. Future work to clarify the natural history of IT withdrawal and its response to symptom management should further aid in elucidation of this pathophysiology and help confirm the safety of the protocol described earlier.

For now, our recommendation is that only patients who have failed IT medication rotation and dose escalation and have persistent, worsening pain and decreased functionality should be considered for IT opioid detoxification until further data on safety and efficacy are confirmed. Patients should express understanding that IT withdrawal has not been extensively characterized and the short-term risks of detoxification vs. the long-term risks of continued IT therapy are not clearly defined.

Patients with IT opioid infusions often have multiple comorbidities that need to be adequately addressed prior to admission for detoxification. At this point, we recommend assessment according to 2007 ACC/AHA guidelines,[91] considering detoxification as an ''intermediate risk surgery'' as autonomic lability may manifest with varying severity. Continuous monitoring of vital signs in an inpatient setting is currently recommended until further data on safety and efficacy of this protocol is confirmed.

FUTURE DIRECTIONS

There is a need for more research on the effects of opioid detoxification in the chronic pain population. These 3 cases demonstrate a surprising result, suggesting that IT medication withdrawal may produce an even milder withdrawal syndrome than systemic opioid withdrawal and that cessation of IT opioid therapy alone may result in improvement in outcomes in selected patient populations. Clinical trials are not only needed to verify the safety and efficacy of long-term systemic and IT opioid administration for non-malignant pain, but also to explore the safety and efficacy of systemic and IT opioid detoxification in those patients who are already on this therapy and are not responding satisfactorily.

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