CASE STUDY

Poor pain relief and possible toxicity from high-dose intrathecal opioid treatment: Report of two cases

Anca Popescu, MD
Rajorshi Mitra, MD
Jane Ballantyne, MD, FRCA

INTRODUCTION

Chronic intrathecal (IT) opioid treatment has proved helpful for the treatment of advanced terminal cancer pain when systemic opioid treatment fails through loss of efficacy or intolerable side effects. The IT opioid dosage is only a small fraction of the oral dose (1/300 for morphine), and side effects such as sedation, constipation, and urinary retention tend to occur less frequently than with systemic administration. This treatment is particularly useful for multifocal, refractory pain. The success of IT opioid therapy in cancer patients and the technological advances that have improved the availability, feasibility, and safety of implanted pumps have prompted the extension of IT opioid therapy into the realm of chronic nonmalignant or nonterminal pain. Patients are now treated this way not only for the last few months of their lives but possibly for many years.

We were briefly involved in the pain care of two IT opioid-treated chronic pain patients during their hospital admission for nonpain-related medical emergencies. In both cases, unusually high IT doses were used and failed to provide analgesia; also in both cases, concomitant endocrine disease complicated the clinical picture. Possible mechanisms for failed analgesia and for toxicity from high-dose opioid therapy are discussed.

CASE 1

A 51-year-old woman was admitted to the hospital complaining of severe occipital headache and neck stiffness, four days after uneventful recovery from nasal endoscopic fat graft obliteration for a persistent cerebrospinal fluid leak secondary to empty sella syndrome. Right parietal intracranial hemorrhage was confirmed by magnetic resonance imaging; she was treated conservatively with steroids and antibiotics and discharged after 15 days with full resolution of headache.

During hospitalization, she had a persistent complaint of severe bilateral lower extremity pain. Pain was shooting in quality, with a stocking distribution, and rated 10 out of 10 on a verbal scale. Pain history was notable for persistent severe peripheral neuropathy (earliest notation in patient history was 1995), initially treated with oral opioids and adjuncts. In 1997, an IT pump was placed and opioid therapy was started. The IT opioid dose was gradually increased to the admission dose: hydromorphone 33 mg per day (66 g oral morphine equivalent) plus fentanyl 2,560 mcg per day (76.8 g oral morphine equivalent). Other pain medications at admission included OxyContin (Purdue Pharma LP, Stamford, CT; 40 mg t.i.d.), Percocet (Endo Pharmaceuticals, Chadds Ford, PA; one to two tablets every four to six hours), oral hydromorphone (2 to 4 mg every 4 hours), gabapentin (800 mg t.i.d.), and baclofen (20 mg t.i.d.). During hospitalization, the preadmission pain regime was continued, and analgesia was supplemented with hydromorphone via patient-controlled analgesia as well as intermittent nurse-administered intravenous morphine. The hospital Pain Service was then consulted because of the failed analgesia and the unusually high opioid doses.

Medical history was complex. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) and empty sella syndrome were diagnosed in 1995. Painful lower extremities were assumed to owe to POEMS. Other significant past medical history included carcinoid tumor of the appendix, polycystic ovary (Stein-Leventhal syndrome), hypertension, hypothyroidism, gout, and hyperlipidemia. Past surgical history included total abdominal hysterectomy and bilateral salpingo-oophorectomy. Medications in addition to those taken for pain were labetalol (200 mg p.o. b.i.d.), captopril (12.5 mg t.i.d.), oral phenytoin (200 mg t.i.d.), allopurinol (300 mg q.d.), oral furosemide (40 mg b.i.d.), oral atorvastatin (10 mg q.d.), levothyroxine (200 mcg q.d.), paroxitine (50 mg q.d.), estradiol (0.05 mcg every 72 hours), triamterene (37.5 mg q.d.)/hydrochlorothiazide (25 mg q.d.), and oral sustained-release potassium

chloride. Significant endocrinological screen on post-admission day nine revealed the following laboratory values: thyroid stimulating hormone 0.33 μU per mL (low), prolactin 18.3 ng per mL (high), adrenocorticotropic hormone 128.0 pg per ml (high), a.m. cortisol 26.2 ug per dL (high), luteinizing hormone < 0.2 U per L (low at postmenopausal range), follicular stimulating hormone 0.6 U per L (low at postmenopausal range). Serum electrolytes were normal.

The Pain Service reduced the patient's IT hydromorphone dose by 10 percent per day, from 33 mg per day to a discharge dose of 8 mg per day. The IT fentanyl dose was unchanged. She was discharged on her preadmission oral pain regime for follow-up with her local pain clinic. Further weaning of the IT opioid was recommended. Intrathecal hydromorphine wean did not cause withdrawal or a change in pain intensity.

CASE 2

A 56-year-old woman was admitted to the hospital after three episodes of loss of consciousness lasting 10 to 15 seconds, associated with stiffening of all extremities. One episode was witnessed in the emergency room, where she had a 10- to 12-second sinus pause followed by spontaneous regaining of consciousness. The patient gave a two-year history of unexplained falls without loss of consciousness. She also reported frequent spontaneous myclonic jerks for the past several years, mostly during sleep. There was no temporal relationship between the falls and the myoclonic episodes. Myoclonus without neural deficit was obvious at the time of admission. The patient was emaciated and frail, with ecchymoses over all extremities. She was lethargic but arousable, and oriented but with poor attention and concentration and flight of ideas. Holter monitoring revealed sinus node dysfunction, and a permanent pacemaker was placed. Hospital course was complicated by development of hemopericardium and pericardial tamponade requiring pericardiocentesis. She was discharged after three weeks with normalized paced cardiac rhythm, improvement in myoclonus, and normalized mental status.

Throughout the hospitalization the patient complained of widespread pain, mostly below the waist, associated with tactile allodynia. Pain was described as continuous, unrelenting, and gripping in character. Pain was rated as an 8 or 9 out of 10 on a verbal scale throughout admission. She had experienced chronic pain since childhood. Scoliosis had been treated with Harrington rod placement when she was a teenager. The pain and scoliosis were disabling, and she was wheelchair bound. She had been treated with oral opioids for the past 28 years. Two weeks before her hospital admission for sinus arrest, an IT pump had been placed. The oral morphine dose before pump placement was 320 mg per day. At the time of admission, IT opioid dose was 15 mg morphine per day (4.5 g oral morphine equivalent), and oral morphine had been continued in controlled-release form, 60 mg before bed. The only adjustment made in her pain regime in the hospital was to discontinue the regular oral morphine.

The patient's medical history was complex. In addition to chronic pain syndrome, she carried diagnoses of bipolar disease, fibromyalgia, hypertension, chronic obstructive pulmonary disease, and Addison's disease. Addison's disease had been diagnosed one year before admission. Cardiac workup one year before admission revealed normal myocardial and valvular function and absence of ischemia. Medications at admission included oral cortisone acetate (25 mg b.i.d.), modafinil (200 mg per day), clonidine (0.1 mg twice a day), hydrochlorothiazide (25 mg per day), atenolol (50 mg per day), bupropion (150 mg b.i.d.), venlafaxine (37.5 mg per day), and Premarin (Wyeth Pharmaceuticals, Madison, NJ).

The patient's pain neither improved nor deteriorated during hospitalization. Myoclonus gradually improved and mental status cleared. The pain remained severe, rated an 8 or 9 out of 10, despite IT opioid therapy.

DISCUSSION

Intrathecal opioid therapy for intractable chronic nonterminal pain is still under considerable scrutiny in terms of its efficacy and safety. Early reports suggest that the therapy improves pain relief and function for a proportion of treated patients, and that the complication rate is low, although complications can be serious. Retrospective case series published between 1985 and 2001 suggest high rates of patient satisfaction (up to 92 percent[1]), good analgesic efficacy (pain reduction up to 60 percent[1-3]), and improvements in mood and function for up to four years.[1-9] More recent prospective studies[10-13] conducted for up to nine years report good analgesic efficacy (25 to 50 percent pain reduction) and improvements in mood and function, but in only a proportion of patients (up to 50 percent of patients fail the treatment for various reasons[11]). Thus, prospective studies report good results, but they are less impressive than the retrospective study results. For ethical reasons, it has not been possible to conduct randomized controlled studies, or even nonrandomized studies with truly comparable controls, although one carefully conducted recent study[13] did use controls (patients failing IT trials and newly presenting patients). System-related problems, including catheter and pump malfunction, dislodgement, and infection occur in up to 30 percent of implants but are usually reversible without removal.[11] Granulomatous catheter mass formation, a potentially disastrous complication of continued IT therapy, may occur in 5 percent of cases and can result in permanent neurological injury.[14,15]

Common side effects include sedation, nausea, edema, and, in male patients, hypogonadism. The side effects are usually controllable and rarely a reason for abandoning the treatment.[13]

Intrathecal opioid therapy has a record of success in literature reports but did not provide good analgesia in the two cases reported here, in which unusually high doses had been reached. In both cases, treatment did not provide the expected improvement in pain relief, systemic opioids were still being used, and the systemic and/or IT opioid treatment complicated the clinical presentation of an endocrine disorder. These case reports add to a growing literature that is helping us understand the limitations of chronic IT opioid therapy, especially in terms of sensible, validated dosing limitations, and precautions associated with concomitant disease.[15,16]

In the first case, the IT opioid dose was exceptionally high (475 mg per day IT morphine equivalent or 142.5 g per day oral morphine equivalent). In the second, dose escalation to 15 mg per day (4.5 g per day oral morphine equivalent) within two weeks was rapid, starting doses usually being lower (2 to 6 mg per day[17]). Could the phenomenon of opioid induced hyperalgesia have interfered with treatment success at these high doses? The propensity of opioids to produce hyperalgesia (as well as analgesia) has been recognized for some time; in fact, as early as 1954, it was noted in animals that high-dose IT opioids had strychnine-like effects.[18] The clinical phenomenon of opioid-induced hyperalgesia, often manifested as generalized allodynia, is increasingly recognized, especially in the context of high-dose intravenous opioid infusions used in intensive care, and after remifentanil anesthesia.[19-22] In the treatment of pain with IT opioids, a hyperalgesia syndrome—painful dose-limiting toxicity characterized by onset of pain and hypersentivitity (allodynia, particularly below the waist, sometimes with myoclonus)—has been reported and is considered a rationale for cautious dose escalation, especially above 20 mg per day.[17] It has been postulated that morphine metabolites, notably morphine-3-glucuronide, acting on glycine receptors, may have strychnine-like effects.[1,23]

Recently, a great deal of experimental work has focused on the phenomenon of opioid-induced hyperalgesia in the hope of elucidating mechanisms of failed analgesia and tolerance during opioid treatment. The role of the N-methyl-D-aspartate receptor in the development of opioid-induced hyperalgesia, opioid tolerance, and neuropathic pain has been recognized.[24-26] The exact mechanism of opioid-induced hyperalgesia—whether dose related, drug related, or somehow related to mode of administration (e.g., worse during IT administration)—remains elusive. Nevertheless, caution should be used when escalating opioid doses, whether IT or systemic, and failed analgesia with worsening physical and psychological status should warn of the possibility that dose escalation is making matters worse.[16] Measures aimed at reducing opioid tolerance (e.g., opioid "holiday," opioid rotation, rotation to methadone, epidural or intrathecal nonopioid therapies such as clonidine or local anesthetic) may be a better choice than persistent dose escalation.[15,16]

Both patients reported on here had underlying endocrine disorders. Although it would be inappropriate to implicate IT opioid therapy in their endocrine disease, one must certainly question the contribution of IT opioid therapy, especially knowing the irrefutable evidence that IT opioids have significant endocrine effects. Opioids suppress the hypothalamopituitary adrenal and gonadal axes and may also have direct adrenal and gonadal effects.[27-30,31] These effects have been described in animals and in humans. In humans, the effects are seen in heroin addicts,[31-36] former addicts in stable methadone programs,[32,33,37] chronic pain patients treated with opioids in the long term,[38-40] and patients treated with IT opioids. Probably because of relatively high cerebrospinal fluid opioid levels directly impacting the hypothalamus and pituitary, clinically important hormonal effects arise most commonly, although not exclusively, during IT opioid therapy.[3,8,13,41-44] Male patients may display loss of libido and energy, impotence, infertility, and depression. Testosterone replacement has been found to be restorative in male patients treated with IT opioids.[34,38,41,42,45] Female patients may display loss of libido, galactorrhea, ammenorrhea, and infertility.[46,47] In addition to gonadal effects, opioids may suppress adrenocorticosteroids,[48-52] and onset of Addison's disease has been reported in one IT opioid-treated patient.[41] The clinical significance of opioid cortisol effects is unclear.

For carefully selected patients—particularly those in whom opioid therapy has been effective but becomes impaired by intolerable side effects—IT opioid therapy can dramatically improve quality of life, function, and pain relief. This does not mean that IT opioid therapy should be considered a panacea for failed analgesia. It will be successful only when patients are carefully selected, doses are carefully titrated (possibly incorporating nonopioids into the IT drug mix), and adverse effects such as neuroendocrine effects are recognized and appropriately avoided or treated. There is still much to be learned about IT opioid therapy, and the cases discussed here raise the question of whether high-dose IT opioid therapy is therapeutic or merely toxic.

Anca Popescu, MD, Department of Neurology, Temple University Hospital, Philadelphia, Pennsylania.
Rajorshi Mitra, MD, Department of Physical Medicine and Rehabilitation, Stanford University Hospital, Stanford, California.
Jane Ballantyne, MD, FRCA, Chief, Division of Pain Medicine, Massachusetts General Hospital Pain Center, Department of Anesthesia and Critical Care, Harvard Medical School, Boston, Massachusetts.

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