CASE STUDY

Safety and tolerability of high doses of intrathecal fentanyl for the treatment of chronic pain

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ABSTRACT

Fentanyl is commonly used systemically or neuraxially for the management of chronic pain. It can be administered intrathecally via implanted pump, but it is generally considered only after trials of intrathecal (IT) morphine and hydromorphone have proven ineffective. Published experience with IT fentanyl is limited, and long-term therapy at relatively high doses has not been described previously. We describe four patients who were treated with IT fentanyl after other analgesic approaches had failed and who gradually underwent dose escalation to levels as high as 20 times those previously reported. Safety and tolerability were maintained during dose titration. Our experience highlights an expanding scope of practice in the use of IT opioids in general and fentanyl specifically and suggests that high-dose fentanyl can be used safely in highly selected patients.

Key words: fentanyl, intrathecal, dose escalation, chronic pain

INTRODUCTION

Fentanyl is a potent μ agonist opioid widely used in anesthesia and pain management. It is commercially available for systemic administration as a solution and in formulations that deliver the drug transdermally or transmucosally. Neuraxial administration may be accomplished via epidural or intrathecal (IT) delivery systems. Although supporting data are limited, long-term IT infusion through an implanted pump is an accepted approach for carefully selected patients with chronic pain, typically those who have not responded satisfactorily to IT morphine and/or hydromorphone.[1-3]

The literature describing the long-term use of fentanyl delivered by IT infusion is limited to case series. IT doses up to 300 μg/d have been reported.[3] Although higher doses are used clinically and the potential outcomes associated with this approach are assumed to be comparable to those observed during neuraxial infusion with other opioids, there are no published observations. We describe four patients with chronic pain whose doses of IT fentanyl were gradually titrated to levels as high as 20 times those previously reported. These cases are relevant to an understanding of both safety and tolerability of IT fentanyl during long-term therapy.

CASE REPORTS

Case 1

A 58-year-old diabetic man was experiencing severe chronic pain from multiple sources. He reported persistent lower back pain and L4-5 radicular pain which began after laminectomy to correct L4-5 stenosis in 1989. Years later, he required a below-the-knee amputation for complications of diabetes and subsequently developed phantom limb pain. He reported constant moderate pain which became severe with activity. There were no other medical or psychiatric comorbidities, and his functioning was markedly impaired by the pain. Examination was consistent with lumbar spinal stenosis.

During this patient's years of pain he underwent multiple trials of opioid and adjuvant analgesics. Trials of oral methadone and hydromorphone, transdermal fentanyl, and injectable meperidine had all yielded opioid-related side effects and minimal pain relief. A trial of IT therapy was recommended, and the patient initially responded well to IT morphine. Gradual dose escalation was needed to maintain adequate pain control, however, and as the dose of IT morphine was increased, he developed multiple medical problems, which were interpreted as

the results of a combination of opioid-related toxicity and his baseline diabetes. These included severe constipation complicated by impaction (and an episode of bowel perforation), mental clouding, somnolence, weight gain, and decreased libido.

Approximately three years ago, the patient was admitted to the hospital to facilitate a switch to an alternative IT infusion. The IT morphine was discontinued and the patient was started on intravenous (IV) fentanyl at a dose of 200 μg/hr, plus 50 μg every 10 minutes as needed. The IV infusion was adjusted to optimize benefit, at which point the infusion was stopped and IT fentanyl was administered using an IV:IT ratio of 1:1. During the next week, the IT fentanyl was rapidly increased to 14,000 μg/d and bupivacaine was added at a dose of 3.52 mg/d. The patient was discharged with good pain control and tolerable side effects.

Over the next three years, the IT fentanyl dose was slowly titrated at an average increment of 20 percent every two months. The patient is currently treated with IT fentanyl at a dose of 24,000 μg/d and bupivacaine at a dose of 7.69 mg/d. Various systemic drug trials have been undertaken in the interim, and, over time, the most helpful supplemental therapy has been a combination of diazepam 20 mg every four hours as needed and meperidine injection 200 mg every four hours as needed. On this regimen of two IT drugs and two supplemental drugs as needed, the patient reports satisfactory pain relief and no side effects, and his ability to function has not declined over the years.

Case 2

A 56-year-old woman reported intense pain and disability related to a 30-year history of low back pain and a nine-year history of pudendal neuralgia. She experienced moderate, constant, burning pain in the lumbar region and buttocks that flared with any activity and prolonged sitting. She could walk 15 feet without stopping and usually used a wheelchair. The examination revealed allodynia in the painful region.

She had received multiple trials of opioids and adjuvant analgesics over the years. Opioid trials included oral methadone and hydromorphone and transdermal fentanyl, all of which provided little benefit. She underwent coccygectomy in 2000 but showed no improvement, and during the succeeding years she had S5 dorsal root ganglion block followed by bilateral S5 dorsal root ganglionectomy, epidural injections, and a trial of spinal cord stimulation. None of these interventions was helpful.

A trial of IT morphine and bupivacaine yielded moderate pain control, and a pump was implanted. Escalation of the morphine dose to 34 mg/d yielded worsening side effects, and in 2004 the IT infusion was switched to fentanyl and bupivacaine, initially at doses of 750 μg/d and 9 mg/d, respectively. There was initial improvement, but this was transitory, and the patient was referred to us for further intervention.

The IT fentanyl was gradually titrated to 4,000 μg/d, at which point the patient reported benefit. This improvement lasted two months, after which the pain again worsened. The IT fentanyl dose was slowly titrated to 7,000 μg/d, and pain control improved. When pain again increased, oral methadone was added, with good effect. For the past year, the patient has been receiving IT fentanyl and bupivacaine, methadone 10 mg five times a day, and gabapentin 300 mg three times daily, a dose that could not be increased due to side effects. Pain control is adequate, she reports no significant side effects, and function has improved—she no longer uses a wheelchair.

Case 3

A 55-year-old woman had an episode of viral (Epstein-Barr) transverse myelitis at C5 in 1981. She recovered to a level of mild quadriparesis, atrophy of the distal muscles of the left upper extremity, and persistent incontinence. Slowly progressive pain became the major problem and was severe below the knees and in her left arm and left abdomen. The pain awakened her from sleep and was exacerbated by standing, walking, and prolonged sitting. Intermittent severe flares of pain occurred spontaneously and resulted in frequent hospitalizations.

Prior therapeutic trials had included opioids and adjuvant analgesic drugs, physical therapy, and acupuncture. None of these therapies yielded substantial pain relief. In 1999, she underwent a successful IT morphine/clonidine trial and a pump was implanted. For five years, she reported acceptable pain control and tolerable side effects while receiving this IT infusion combined with oral methadone at a dose of 20 mg three times daily, nortriptyline 50 mg three times daily, tizanidine 4 mg three times daily, and access to supplemental oral transmucosal fentanyl citrate 1,200 μg as needed up to three times daily. In 2004, pain flared and she required hospitalization. The IT morphine was switched to IT fentanyl; an infusion was initiated at 40 μg/d, and the patient reported that this dose provided good pain control without side effects. Several months later, pain again flared. Bupivacaine and clonidine were added to the IT infusion and the oral medications were adjusted. Pain control remained inadequate and she was referred to us for further interventions.

Given the lack of side effects from the IT infusion, the IT fentanyl was initially titrated. Pain control improved at a dose of 2,000 μg/d. There were still no significant side effects. Several months later pain worsened, and the dose of IT fentanyl was slowly titrated to 5,967 μg/d. Pain control was satisfactory for about one year. Recently, the patient experienced a severe pain flare, and the IT fentanyl was replaced by an IT trial of ziconotide (5,400

μg/d) combined with transdermal fentanyl patches (300 μg/hr patches changed every three days), oral transmucosal fentanyl citrate (1,600 μg, usually once daily), and duloxetine (40 mg daily). The pain improved, but due to changes in mental status the dose was reduced to 4,800 μg/d.

Case 4

A 58-year-old man had been experiencing slowly progressive pain since becoming paraplegic after traumatic spinal cord injury at the T7 level almost 30 years ago. At the time of his first visit, he was wheelchair bound and reported excruciating back pain radiating to the abdomen and pelvis. The pain awakened him from sleep and interfered with all activities. There were no significant medical or psychiatric comorbidities. Physical examination was significant for muscle atrophy and spastic paralysis of the lower extremities.

Prior treatments for the pain had included systemic opioid analgesics, including morphine, oxycodone, methadone, and transmucosal fentanyl, and trials of adjuvant analgesics. The patient reported inadequate analgesia and intolerable side effects from many medications. Prior trials of spinal injections and physical therapy had also yielded no benefit. In 1999, a trial with IT baclofen was effective for spasticity, and a pump was implanted. The pain continued to worsen, and approximately one year later morphine was added to the pump. Over the subsequent year, the dose of IT morphine was gradually increased to 10 mg/d. The patient developed drowsiness and progressive constipation, and the morphine was switched to fentanyl.

The IT fentanyl was initiated at a dose of 600 μg/d. The IT morphine was stopped and oral morphine was given to supplement the IT fentanyl. The fentanyl dose was increased gradually, and as pain control improved the oral morphine dose was reduced. After approximately one month, the dose of IT fentanyl had reached 6,000 μg/d and the patient reported good pain control. Although he denied typical opioid side effects, spasticity increased substantially, and he requested a switch back to IT morphine. This was accomplished, and efforts at pain control via combined IT infusion and systemic analgesics continued. Currently, the patient is reporting incomplete pain control while receiving IT morphine at a dose of 7 mg/d and oral transmucosal fentanyl citrate at a dose of 1,600 μg six times daily.

DISCUSSION

These cases exemplify a small subset of patients with severe and intractable chronic pain. Numerous analgesic interventions had been tried over a period of years in each case before the decision was made to implement neuraxial infusion. IT morphine or morphine combined with other drugs was ineffective, and the conventional practice of opioid rotation was undertaken in the hope of identifying a drug with a more favorable balance between analgesia and side effects.[1,2] Fentanyl is often empirically selected for a trial in such circumstances, despite limited published data documenting outcomes during long-term IT fentanyl infusion.

Published descriptions of IT fentanyl have included patients receiving a maximum dose of approximately 300 μg/d.[3] The present cases substantially expand on published experience, demonstrating the potential for safe and effective therapy at doses up to 20 times higher. Neither early side effects due to the presumed systemic redistribution of the IT drug nor any evidence of fentanyl-induced chest wall rigidity were observed in any of these cases. With the exception of one patient with spinal cord injury, whose baseline spasticity worsened with high-dose IT fentanyl, side effects were those anticipated for opioids.

After IT administration, fentanyl rapidly equilibrates in the general circulation, resulting in significant plasma levels. Indeed, one study demonstrated that plasma fentanyl concentrations were similar two hours after equal doses of IV and IT fentanyl.[4] Hence, rapid clearance into the systemic circulation may result in lower-than-expected concentrations at the level of the posterior spinal horn when single doses of fentanyl are administered. Nonetheless, the analgesia produced by fentanyl can be more efficacious with the IT route than the IV, even with equal doses.[5] The reasons for this are not entirely clear, but it could potentially be related to differences in drug concentrations reaching active sites in the spinal cord and brain.[6] Studies that measure pain while concurrently assessing fentanyl concentrations systemically and at several neuraxial sites during steady-state infusion would be needed to better understand these differences.

Patients who undergo pump trials have to be evaluated for psychiatric disorders, including depression and drug abuse. Patients with depression, a common comorbidity in patients with chronic pain, may develop psychotic features or anxiety and may not tolerate the pump.[7] A recommended practice is to order an evaluation by an experienced pain psychologist to address these specific issues before the trial is started. In the four cases that we are presenting, there was no history of significant depression or drug abuse in any patient. Patients were monitored for the possibility of misuse and diversion of medications at every visit. There was no evidence of multiple prescriptions, early calls for refills of medications, or any other abuse-related issues in any of the four patients.

Although this case series illustrates that high doses of IT fentanyl can be used safely for the treatment of chronic pain in patients who have not responded satisfactorily to conventional treatment, a survey shows that it is the

drug of preference of only 1 percent of the physicians who responded.[2] Larger studies are needed to confirm our observations.

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