Letters

Oral Transmucosal Fentanyl and Sufentanil for Incident Pain

To the Editor:

Fentanyl has been available for many years as a synthetic opioid analgesic, and is mainly used in the operating room. Its use in chronic pain has been limited by its short duration of action, affording approximately 40 minutes of pain relief.

Fentanyl and the related opioid, sufentanil, are much more lipid soluble than many other opioids,[1,2] and consequently, both can be delivered through mucous membranes, either oral transmucosally or sublingually.[3,4] Only parenteral preparations of fentanyl and sufentanil are available in Canada, and there is a lozenge preparation available in the United States, which is approved for the management of breakthrough pain in cancer patients,[4] and for premedication in children.[5] This lozenge demonstrates that fentanyl lacks the bitter taste associated with some other opioids. Fentanyl and sufentanil should offer fast onset analgesia when given sublingually or oral transmucosally, despite their short durations of action, and both might be useful for breakthrough pain. Described here are six cases where this method of administration has been useful.

Case 1

A 42-year-old Caucasian woman with metastatic carcinoma of the colon was referred with multiple episodes (up to 25 daily) of watery stools associated with intestinal cramps and continuous pain in the lower right quadrant. She was titrated up to 225 μg/hour of transdermal fentanyl (patches changed every three days) for pain control, with oral hydromorphone 4 mg to 8 mg every four hours as needed for breakthrough pain. Anti-spasmodics, such as diphenoxylate hydrochloride and hyoscamine sulfate, were tried with only temporary relief of intestinal cramps and diarrhea. Octreotide 100 mg subcutaneously twice daily was started with good effect in reducing bowel movements to three times daily. However, the pain of intestinal colic became difficult to control with maintenance analgesia only, and "rescue" doses of oral or subcutaneous hydromorphone were slow to take effect. Sufentanil 50 μg/ml was started at 0.05ml to 0.15 ml (2.5 μg to 7.5 μg) sublingually, hourly as needed to control the pain of intestinal cramps. The patient reported a pain intensity of 10 of 10 (0, no pain; 10, excruciating pain) at the height of the colic, which was reduced to 5 within six minutes of taking 7.5 μg sufentanil sublingually. Sublingual sufentanil had a faster onset of action (6 minutes versus 12–15 minutes with subcutaneous hydromorphone) and gave greater relief than subcutaneous hydromorphone injections with no clouding of consciousness. Cost of the sufentanil solution sufficient to last twelve days, taking the injectable solution and dispensing it into 10ml bottles with a dropper, was $87.20 (Canadian), compared to the hydromorphone parenteral solution at $274.00 (Canadian).

Case 2

A 51-year-old Caucasian woman with Stage 4 carcinoma of endometrium and painful thrombophlebitis migrans in her right arm, was referred for symptom control. Nonsteroidal anti-inflammatory drugs, and, later, anticoagulants, did not relieve the pain of the spasms. Controlled-release morphine, 30 mg every 12 hours, caused dysphoria and she was changed to transdermal fentanyl 50 μg/hour with hydromorphone 2 mg to 4 mg orally or subcutaneously every four hours as needed for breakthrough pain. However, sudden onset spontaneous painful spasms in her superficial

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veins were scored at a pain intensity of 10 of 10, and lasted for more than 30 minutes at a time. She was prescribed sufentanil 50 μg/ml, 5 μg to 7.5 μg sublingually, hourly as needed for sudden onset pain. She reported onset of action was 4 to 6 minutes, duration of pain control was 35 minutes, and reduction of pain intensity was 4 of 10. This was better than she could achieve with hydromorphone (onset of action 15 minutes) and was associated with less nausea. As her illness progressed, the sufentanil was titrated up to 12.5 μg sublingually, hourly as needed, to control her vascular spasm pain and was occasionally combined with oral hydromorphone for continuing pain relief after the sufentanil analgesia wore off.

Case 3

A 53-year-old Caucasian woman with carcinoma of the breast, multiple bony metastases, and pulmonary emboli was referred for pain control. Long-acting morphine 75 mg every 12 hours caused excessive sedation; she was started on transdermal fentanyl and titrated to 175 μg/hour using 50 mg of short-acting morphine four hourly, as needed, for breakthrough pain. Incident pain was a major problem because of her bony metastases, and she had received multiple courses of chemotherapy and maximum radiotherapy to all sites. She was initially given sublingual fentanyl 50 μg/ml, 0.2–0.4 ml (10 to 20 μg) every four hours as needed for incident pain, such as rising from bed in the morning and getting out of her chair to go to the bathroom. Pain intensity was reduced from 8 of 10 to 4 of 10 using the sublingual fentanyl. The onset of analgesia following a dose was approximately 6 minutes. As her pain increased, the volume of fentanyl became cumbersome and she was switched to sublingual sufentanil. She required 12.5 μg to 15 μg of sufentanil to reduce her pain score, sometimes combined with a breakthrough dose of short-acting morphine 50 mg so that analgesia could continue after the sufentanil effect had worn off.

Case 4

A 58-year-old Caucasian woman presented with severe left arm pain associated with left-sided chest pain related to stress and exercise. Several years previously, she had received trauma to her cervical spine from a heavy object during an accident at work, after which she had suffered many neck spasms and severe migraines. She had Crohn's disease, was intolerant of anti-inflammatory medications, and was also severely allergic to local anesthetics. Cardiologically, a stress test was negative and a cardiologist felt that her chest pain was not of cardiac cause. However, the pain partially responded to verapamil SR 240 mg daily, suggesting that it was due to some degree of coronary spasm. Nifedepine and nitrolingual spray could not be used because they caused exacerbations of her migraines. The episodes of chest and left arm pain caused her to pace her floors at night; acetaminophen/codeine and acetaminophen/oxycodone combinations were of little value and lorazepam had little effect. Sublingual fentanyl 50 μg/ml, 0.05 to 0.1ml (2.5 μg to 5 μg) every two hours as needed, was prescribed and she reported that her pain, which was a 10 during these episodes, was reduced to a 2 within 10 minutes of taking the medication. Over the subsequent months, possibly due to reduced anxiety, her consumption of fentanyl fell; 10mls of liquid fentanyl 50 μg/ml lasted at least 6 months.

Case 5

A 51-year-old Caucasian woman was referred for pain control after a nine year history of severe back pain, for which she had undergone two back surgeries involving a posterior lateral nerve root decompression of L5–S1 on the right side and a fusion. Despite vigorous physiotherapy, she noticed onset of back pain similar to before the operation several weeks after the back surgery. She restarted her anti-inflammatory medication and was placed on carbamazepine 400 mg daily for leg spasms, which were becoming increasingly troublesome. She found it increasingly painful to rise from her bed in the morning, to rise from naps during the day, and to stand for any length of time in her kitchen to prepare meals. Sublingual fentanyl, at 50 μg/ml, 2.5 μg to 7.5 μg was started, every two hours as needed for incident pain. She reported that the 90 minutes it took her to rise from her bed in the morning, even after taking an acetaminophen/oxycodone tablet, had been reduced to 10 minutes by substitut-

ing sublingual fentanyl 5 μg, and that she was able to become more active more quickly and overcome the pain. She continues to use fentanyl liquid sublingually, and requires a prescription of 20 ml of 50 μg/ml fentanyl only every 6 months.

Case 6

A 50-year-old Caucasian woman had a several year history of severe back pain since a fall at work in 1988. A few months after her fall, she had a diskectomy but continued to have severe back pain for which she took up to four acetaminophen/oxycodone tablets daily. Although she remained as active as possible, she experienced severe restlessness of her legs and painful leg spasms, which particularly affected her at night. Baclofen 20 mg up to 4 times daily helped to reduce the frequency of spasms and reduced the restlessness of her legs. Her quality of life was deteriorating due to lack of sleep. Fentanyl liquid 5 μg to 15 μg every two hours as needed was prescribed for the restlessness and spasms, and she reported that the medication was effective in abolishing the spasms within approximately 5 minutes. Intensity of the spasms was scored at 9 out of 10 and was reduced to 4 out of 10 after medication. She was able to resume sleep within 30 minutes of taking the liquid, and spasms did not usually occur during the remainder of the night. She required only 20mls of fentanyl 50 μg/ml every 6 months for maintaining her quality of life.

Comment

Six patients, three with cancer pain and three with noncancer pain, used sublingual fentanyl or sufentanil to manage breakthrough pain. The onset of action was described as faster than a subcutaneous injection of hydromorphone and none experienced sedation. The chronic noncancer patients described above have been maintained on fentanyl liquid for incident pain with no escalation of dose for 8 years.

The bioavailability of these drugs when administered sublingually is likely high, suggesting that analgesic levels similar to those obtained by intravenous delivery may be achieved by this route, and recent literature[6,7] has demonstrated dose proportionality over dose ranges. Despite short duration of action, oral transmucosal fentanyl had been effective as "rescue" analgesia for breakthrough pain in cancer patients on transdermal fentanyl.[4] This may suggest that rapid onset of analgesia may be effective in "winding down" the pain experience, resulting in a shorter duration of pain exacerbation.

This sublingual method of administration could be used in long-term care settings, where dressing of bedsores may involve intense incident pain, and be taken in conjunction with conventional analgesic "rescue" medications to enhance speed of onset of pain relief. It would be helpful if studies were established to look at the use of sublingual fast onset analgesics, which may increase our scope in providing more effective and timely pain control to patients who have both cancer and severe noncancer pain.

Jackie Gardner-Nix, MB BS, PhD, MRCP (UK)
Wasser Pain Management Center, Mt. Sinai Hospital and Pain Management Program
Sunnybrook & Women's College Health Sciences Center, Toronto, Ontario, Canada

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Pamidronate in Incident Pain Due to Bone Metastases

To the Editor:

Pain due to bone metastases frequently occurs in cancer patients, and is often severe and resistant to available therapies. Patients with bone metastases commonly experience intermittent exacerbations of severe pain related to activity, which occur against a background of continuous or baseline pain. This type of breakthrough pain has been defined as incident pain. It is generally predictable and is an independent contributor to impaired functioning and psychological distress.[1]

To treat breakthrough pain, an increase in the round-the-clock analgesic dose can be tried if end-of-dose failure is recognized. However, in most cases, an increase in the total daily dose will result in excessive sedation during rest. Other options have been proposed to treat the painful event once it occurs.[2]

Pamidronate, a second generation aminobisphosphonate, can be considered an important therapeutic tool in association with other therapeutic modalities in the treatment of metastatic bone disease with marked osteolysis such as breast cancer. Randomized controlled trials have demonstrated that bisphosphonates reduce both skeletal events and pain.[3] By reducing osteoclastic activity, bisphosphonates inhibit bone resorption. Although the effects of bisphosphonates on calcium homeostasis are well known, their mechanism of action has not yet been completely clarified. Recent studies suggest that this class of drugs also may be able to modify the natural history of cancer by their effects on direct or indirect tumor products. For these reasons, pamidronate may potentially be useful in reducing incident pain due to bone metastases.

Case Report

A 72-year-old woman with metastatic breast cancer was admitted to a pain relief and palliative care unit with severe back pain radiating to the legs. She had known metastases to the lumbar vertebral bodies and had received several courses of chemotherapy. Radiation therapy had already been administered to the painful areas. Bone scintigraphy demonstrated uptakes in lumbar and thoracic vertebral bodies. She had been bedridden for some weeks for her pain. On physical examination, the patient was in distress caused by pain and immobility. No laboratory abnormalities were found. Previous treatment prior to admission included anti-inflammatory drugs and codeine occasionally. No significant relief had been achieved with these medications. Courses of pamidronate at 90 mg a month were planned, and morphine was titrated to achieve analgesia at rest. Morphine doses were rapidly increased up to 120 mg per day to improve mobilization, at least in bed, for sore prevention. Ketorolac 60 mg daily was added to the therapeutic regimen. However, pain on movement remained difficult to control, and the patient remained bedridden.

During the following monthly admissions, pamidronate was intravenously administered in doses of 90 mg. Doses of morphine were increased up to 300 mg per day to allow movement, but this resulted in severe drowsiness. Morphine in doses of 240 mg per day was prescribed for home.

When the patient was admitted to the pain relief and palliative care unit for a clinical reassessment and the fourth pamidronate infusion, she was, surpisingly, walking with the help of a stick. Morphine doses could be progressively reduced down to 90 mg daily, and after two days she was discharged home with this morphine dose. Phone contact was maintained to monitor the clinical situation. She was able to maintain her autonomy and could cook during the Christmas holidays. This optimal pain relief was maintained at the following admission. On that occasion, a bone scintigram demonstrated a small change in radionuclide accumulation at the sites of vertebral metastases, when compared with the findings prior to the first admission to the pain relief and palliative care unit.

Thirteen months after starting pamidronate the patient had optimal functional activity and was walking and working using morphine 120 mg daily. This good outcome occurred despite signs of progression of disease with diffuse hepatic metastases.