Journal of Pain & Relief
ISSN: 2167-0846

Delicou et al., J Pain Relief 2013, 2:3
DOI: 10.4172/2167-0846.1000125

Case Report Open Access

Hyper-Acute Toxic Delirium in a Patient Using Transdermal Fentanyl

Delicou S*, Kourouni I, Samarkos M, Kouzis P and Mantzourani M

1st Department of Internal Medicine, Laikon University Hospital, Athens, Greece

Abstract

The unpredictable, recurrent, intense, and frequently persistent nature of pain associated with sickle cell disease poses a difficult challenge in terms of management. The long-term treatment of non-malignant pain with opioids has traditionally been a matter of debate globally due to the perceived fears of addiction, toxicity and tolerance. In the past decade, opioid analgesics have been advocated by some medical professionals for the treatment of refractory non-malignant pain. For patients with SCD and chronic pain, the pain differs from other forms of chronic pain (e.g., cancer pain) in that sickle cell pain is typically associated with episodic and chaotic waxing and waning acute pain on top of chronic pain. There is also likely to be a larger component of neuropathic pain, peripheral and central sensitization to pain, and opioid hyperalgesia in patients with SCD. In addition, unlike individuals with cancer who have pain, patients with SCD live with this pain for decades?

Transdermal fentanyl (Duragesic) is indicated for patients who require continuous opioid administration for the treatment of chronic pain that cannot be managed with other medications such as short-acting opioids on an as-needed basis or non-opioid analgesics. Pain should be under relatively stable control prior to the initiation of transdermal fentanyl, since meaningful pain relief is not obtained until 12-16 hours after application. We describe here the case of a fifty-year-old woman with sickle cell/beta thalassemia complicated by multiple painfull crisis admissions and suspected opioid abuse, who manifested unusual psycho-mimetic reactions after the first-time application of transdermal fentanyl.

Keywords: Sickle cell disease; Transdermal fentanyl; Delirium

Case Report

Our patient is a fifty-year-old woman, 80 kgs, with S/b thalassemia disease complicated by multiple pain crisis admissions for severe chronic pain and suspected analgesic abuse. She was under gabapentin (600 mg/8 h) for pain management for the last two years. During the past six months before her current admission she averaged four hospitalizations. Her last admission was complicated with superficial popliteal vein thrombosis and possible superior vena cava syndrome for which she underwent red blood cell exchange transfusion. Throughout these admissions her pain was relieved with pethidine 10 mg every 4 hours i.v, NSAIDS and hydration. HbS concentration decreased to 21% from 82%. Her analgesic medication after discharge has been a combined regimen of paracetamol and codeine (500 mg/tb+30 mg/tb) and continuation of her gabapentin (600 mg/8 h) as usual.

Five days after discharge she referred to a pain management center and transdermal fentanyl (TTS 75 μg/48 h) was suggested for both acute and chronic pain control (neuropathic). Eight hours after the use of transdermal fentanyl she got admitted to our hospital with irritability, anxiety, fear, depression, abdominal cramping, deep bone pain, muscles aches and increase of her usual pain. She could hear her dog speaking, urging her to come to the hospital and she was seeing her husband close to her, which was not the case. Neurological examination revealed no gross abnormality. Other life threatening abnormalities were quickly evaluated with pulse oximetry, ABGs and basic laboratory evaluation. Because of the patient's known history of S/B thalassemia, an extended work-up took place. A brain CT was negative for acute infarct or hemorrhage and positive only for old lacunae infarcts of limited extension. A urine sample was sent for toxicology screen based upon the suspected history of analgesic abuse in order to rule out any other cause of intoxication. Toxicology screen came back negative.

After reviewing the patient's medication it was apparent that the only change made in her medical regimen was the fentanyl patch and the paracetamol (500 mg)/ codeine (30 mg) discontinuation. All of her other medication had been used for prolonged periods in the past without complications. The fentanyl patch was discontinued. Over the next 12 hours incremental doses of pethidine were given and hydration with D/W 5% was administered.

Next morning she became fully awake and co-operative. She was alert, with clear and appropriate speech but she was not able to recollect the previous event. Later that day, a detailed psychiatric history was taken from the patient who revealed that she had experienced a depressive episode in the past 9 months during receiving treatment with peg- interferon for hepatitis C. She remained in the hospital for a prolonged period in an effort to control her pain and to downgrade both her pethidine needs and analgesic seeking behavior. Discharge medications included quetiapine and lorazepam [1].

Discussion

Sickle cell anemia is a progressive hemoglobinopathy producing chronic hemolytic anemia, micro vascular thrombosis, ischemic pain, tissue infarction, decreased quality of life, and ultimately shortened life expectancy. Painful events are the most common manifestation of SCD. Pain in SCD [1] can be acute, chronic or mixed, can be related to tissue injury (nociceptive), nerve injury (neuropathic), or causes unknown (idiopathic).

The management of pain in sickle cell disease (SCD) has never been viewed with a straightforward approach by many practicing hematologists, pain experts, or generalists, especially for the adult patient. In particular, major depression and chronic pain frequently coexist [2], and both conditions must be addressed to maximize the treatment response for either disorder. In addition to the psychological effects of inadequately treated pain, patients have the added stress of continually searching for effective pain relief, resulting in frequent

***Corresponding author:** Sophia Delicou, Clinical Hematologist, 1st Department of Internal Medicine, Laikon University Hospital, Athens, Greece, Tel: +307012898; E-mail: sophiadelicou@myoperamail.com

Received July 15, 2013; **Accepted** December 10, 2013; **Published** December 12, 2013

Citation: Delicou S, Kourouni I, Samarkos M, Kouzis P, Mantzourani M (2013) Hyper-Acute Toxic Delirium in a Patient Using Transdermal Fentanyl. J Pain Relief 2: 125. doi:10.4172/2167-0846.1000125

emergency room visits and episodic care. This cycle can lead to depression, which is highest among the chronically ill and is often no recognized or addressed.

Many patients experience both anxiety and depression, and have difficulty forming and maintaining both interpersonal and patient-physician relationships.

Adults with SCD experiencing chronic pain, manage it by daily use of opioids. Some may exhibit tolerance to opioids [3]. Understandably, some patients whose pain is managed poorly, try to persuade medical staff to give them more analgesic, engage in clock-watching, and request specific medications or dosages. Our patient therefore obtained analgesia that resemble drug seeking behavior by medical staff. Opioid use disorder [4] is characterized as continued use of opioids despite significant opioid-induced problems. Opioid use disorder can result from the misuse of prescribed opiate medications or from illicit use of the drug. Opiate medications are very effective for the treatment of acute and chronic pain, but have the potential to be misused. Chronic use of pethidine [5] and other opioid agonists may result in an increased sensitivity to pain, which may develop within a month of initiating chronic opioid therapy. On top of these, our patient was under peg-interferon [6] treatment for the past 9 months associated with severe depressive episodes. She revealed though that she had suicidal ideation in the previous months with no definitive suicidal plan.

Delirium and confusional states [7] are among the most common mental disorders encountered in patients with chronic medical illness. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a medical condition, substance intoxication, or medication side effect.

It is usually multifactorial [8], with the most common etiologies being un controlled pain, medications such as opioids, anti-cholinergic drugs, steroids, antipsychotics), polypharmacy, drug withdrawal, infections, fluid imbalances (dehydration, overload) and electrolyte imbalances (hypercalcemia). The overall burden of a chronic illness increases the person's vulnerability for delirium.

Drugs that are agonists or antagonists of a number of other neurotransmitters can produce delirium-like effects [9,10], although the precise role of these neurotransmitter systems is difficult to determine. Cerebrospinal fluid (CSF) studies of patients with delirium reveal alterations in neuropeptides (eg, somatostatin), endorphins, serotonin, norepinephrine, and GABA, among others. However, it is difficult to exclude the confounding effects of underlying illness or dementia.

Pro-inflammatory cytokines [11,12] such as interleukins and tumor necrosis factor alpha also may have a role in the pathogenesis of delirium. These agents have strong CNS effects when injected into experimental animals or when administered for therapeutic purposes (e.g., interferons in chronic hepatitis). Cytokine activation may account for delirium (particularly hyperactive forms of the disturbance) in situations such as sepsis (where mental changes may actually precede fever), cardiopulmonary bypass and acute hip fracture [13]. In the pathogenesis of sickle cell disease abdorminal levels of activators of endothelial cells, macrophages, and other blood cells have been reported and it has been suggested that levels of cytokines and other cell agonists may be used as a measure of clinical severity in SCD [14]. As such, our patient's profile gathers a significant number of these characteristics, thus we can only speculate as to the precise triggering events. Hypoxia, hypotension and anemia are included because of her known past medical history. Sickle cell itself predisposes our patient in episodes of extreme pain when under hypoxemic or dehydrating conditions. Her pain treatment until recently included large doses of pethidine, which may have caused hypoventilation and hypoxemia. We cannot exclude a withdrawal to pethidine as a cause of her altered sensorium as the rest of her symptomatology was also indicating that. We do not think though that there is a possibility of a drug reaction to her other medications, as all of these, except the transdermal fentanyl patch, were continued after the resolution of her delirium.

Our literature search revealed two case reports of acute toxic delirium after the use of transdermal fentanyl patch. Steinberg et al. [15] describe acute toxic delirium in an elderly patient with renal insufficiency who experienced poor pain control and developed an acute delirium while receiving transdermal fentanyl patch for 24 days and who came back to normal one day after the patch was removed. Kuzma et al. [16] described a case of acute toxic delirium in a 14 years old pediatric patient with metastatic adenocarcinoma of unknown origin, metastatic to the liver and skeleton. Another case in literature described a single case report of acute delirium that occurred after intravenous administration of fentanyl (100 μg). This patient recovered back to normal shortly after she received naloxone [17]. The last report describes a case in which acute delirium followed general anesthesia during which the patient also received droperidol and epidural fentanyl. In this instance, no naloxone was administers and the patient recovered gradually over 2 days.

Our patient with S/b thal disease who experienced poor pain control and developed an acute toxic delirium after the first time she received transdermal fentanyl in doses of up to TTS 75 μg/48 h. We realize that she has many predisposing factors to manifest delirium but it seems that fentanyl acted as the critical triggering factor leading to it.

Clinicians who prescribe transdermal fentanyl should be aware of this potential complication and act appropriately when a case like this comes up again. In sickle cell disease transdermal fentanyl patches are effective in chronic pain. These patches are easy to administer and contain multi-day dosage, but stable plasma levels may not be reached for 12 hours after application. The main disadvantages of the patches are that analgaesia is slow in onset and difficult to titrate against response, and that a residual depot is left after removal of the patch [18].

References

1. Stuart MJ, Nagel RL (2004) Sickle-cell disease. Lancet 3654: 1343-1360.
2. Hasan SP, Hashmi S, Alhassen M, Lawson W, Castro O (2003) Depression in sickle cell disease. J Natl Med Assoc 95: 533-537.
3. Ballas SK (2007) Current issues in sickle cell pain and its management. Hematology Am Soc Hematol Educ Program 2007: 97-105.
4. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB (2006) Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med 166: 2087-2093.
5. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, et al. (2002) Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 17: 173-179.
6. Reichenberg A, Gorman JM, Dieterich DT (2005) Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. AIDS 19: S174-S178.
7. Caraceni A, Luigi G (2011) Delirium: Acute confusional states in palliative medicine. Oxford University Press.
8. Aldemir M, Ozen S, Kara IH, Sir A, Baç B (2001) Predisposing factors for delirium in the surgical intensive care unit. Crit care 5: 265-270.
9. Stagno D, Gibson C, Breitbart W (2004) The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. Palliat Support Care 2: 171-179.

10. Burns A, Gallagley A, Byrne J (2004) Delirium. J Neurol Neurosurg Psychiatry 75: 362-367.

11. van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, et al. (2008) Time-Course of Cytokines during Delirium in Elderly Patients with Hip Fractures. J Am Geriatr Soc 56: 1704-1709.

12. Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, et al. (2006) Serum Biomarkers for Delirium. J Gerontol A Biol Sci Med Sci 61: 1281-1286.

13. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C (2008) Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res 65: 229-238.

14. Steinberg MH, Rodgers GP (2001) Pathophysiology of sickle cell disease: role of cellular and genetic modifiers. Seminars in hematology. WB Saunders.

15. Steinberg RB, Gilman DE, Johnson F 3rd (1992) Acute toxic delirium in a patient using transdermal fentanyl. Anesth Analg 75: 1014-1016.

16. Kuzma PJ, Kline MD, Stamatos JM, Auth DA (1995) Acute toxic delirium: an uncommon reaction to transdermal fentanyl. Anesthesiology 83: 869-871.

17. Williams-Russo P, Urquhart BL, Sharrock NE, Charlson ME (1992) Post-operative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 40: 759-767.

18. Delicou S, Konstantinos M (2013) Pain Management in Patients with Sickle Cell Disease-A Review. Hematology.