Craving Behavior from Opioid Addiction Controlled with Olanzapine in an Advanced Cancer Patient: A Case Report

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Abstract

Opioid addiction, although uncommon in cancer patients, can be a significant challenge for optimal pain management in certain patients. We present a case of a 59-year-old man with advanced colon cancer whose compulsive craving for the buccal tablet of fentanyl citrate (BTFC) was improved with the use of olanzapine. He was hospitalized for abdominal pain caused by disease progression. He had visited several times at outpatient follow-up to obtain a prescription for BTFC because he took all medications before the appointed times. After admission, intravenous infusion of oxycodone and opioid rotation were applied to the patient to control his pain. However, he complained that the pain was not relieved at all and persistently asked for only BTFC 7 to 15 times per day. With the diagnosis of opioid addiction, the transdermal buprenorphine patch was applied, but was ineffective for controlling the addictive behaviors. Finally, olanzapine (10 mg/day per os), a dopamine receptor antagonist, was given to control the craving behavior because psychological dependence is mediated by the dopaminergic system. Three days later, opioid craving was reduced from five to one on a 5-point Likert scale. The pain was well controlled to numeric rating scale 1 or 2 without cravings for BTFC. Craving behavior as a result of opioid addiction may be controlled with olanzapine. Further prospective studies on this issue are warranted.

Keywords: addictive; analgesics; behavior; neoplasms; olanzapine; opioid

Introduction

ADVANCED CANCER PATIENTS suffer from diverse physical and psychological symptoms including pain, constipation, and depression.[1,2] Although opioids are an essential medication for cancer patients suffering from pain, the chronic use of opioids may result in addiction. There is growing evidence that chronic opioid use can result in these behaviors including in a palliative care setting.[3,4]

Addiction is associated with physical and psychological dependences. Although these terms are often confused by health providers, they are distinct phenomena. Physical dependence is considered a physiologic response with involvement of norepinephrine, and does not have a causal relationship with opioid addiction. In contrast, psychologically dependent patients exhibit one or more the characteristics of impaired control over drug use, continued use despite harm, compulsive use, and cravings.[5] Psychological dependence is mediated by the dopaminergic system. The dopamine D2 receptor availability and dopamine release are decreased in opioid-dependent subjects.[6,7] Recently, several dopamine gene variants are found to be associated with protection or risk for opioid dependence.[8]

Olanzapine is a second-generation atypical antipsychotic that antagonizes subtypes of D2/D4 receptors from the D2-like family. Olanzapine has been reported to reduce cravings and consumption in alcohol-addicted patients.[9] Given the common mechanism for opioid addiction, olanzapine may be a useful treatment for opioid-addicted cancer patients. However, previous studies on the efficacy of olanzapine have only indicated that it is effective in reducing the cravings of noncancer patients for alcohol,[10] heroin,[11] and cocaine.[12,13]

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There is no study on using olanzapine to treat opioid-addicted cancer patients.

In this study, we report a case of an opioid-addicted terminal cancer patient who had suffered from strong craving behavior that was controlled by olanzapine.

Case Description

A 59-year-old man with advanced colon cancer resistant to all conventional chemotherapy was hospitalized for abdominal pain and general weakness. The patient was a current smoker who had 20 pack-years of tobacco history and had moderate alcohol intake. He denied a history of illicit drugs such as marijuana, cocaine, and heroin. On the baseline mental status examination, he was slightly anxious and otherwise was normal with coherent thought process. His medical history revealed only medically controlled hypertension. The pain was dull aching in nature and was considered to be caused by metastatic lesions in the liver and abdominal lymph nodes. The pain intensity was severe and measured at a level of numeric rating scale (NRS) 8. He had received a low dose of opioid since a year ago. During the past 1 month, he had been on a fentanyl transdermal patch 75 μg/hour for background pain and on a buccal tablet of fentanyl citrate (BTFC; Fentora®; Cephalon, Inc., Frazer, PA) 400 μg for breakthrough pain episodes (morphine equivalent daily dose [MEDD] = 800 mg/day [150 mg/day for the background dose and 650 mg/day for the cumulative breakthrough dose]). During outpatient follow-up, he had visited several times to obtain a prescription for BTFC because of frequent breakthrough pain. He did not want to escalate the dose of fentanyl transdermal patch and took all BTFC before the appointed times.

After admission, continuous intravenous infusion of oxycodone (100 mg/day) was additionally prescribed for abdominal pain (MEDD = 1100 mg/day). However, he complained that his pain was not relieved at all even when he was given a dose of 200 mg/day of oxycodone the next day (MEDD = 1400 mg/day). Although the hyperalgesia syndrome from high-dose opioid use was considered, the characteristics and severity of pain were not changed while the dose of oxycodone rapidly increased. Subsequently, opioid rotation using intravenous morphine or fentanyl was attempted without success. He persistently asked for only BTFC 7 to 15 times per day, which was a similar dose before hospitalization. BTFC only lulled the craving for 2 to 3 hours. At this time, the MEDD was ~1200 to 1600 mg/day.

The physician referred the patient to a psychiatrist for BTFC obsession, and the patient was diagnosed with opioid use disorder categorized as addiction. He was classified into the severe category by meeting 7 of the 11 checklist items: continued opioid use despite having social/interpersonal problems; tolerance (higher MEDD); used larger amounts (higher MEDD and frequent outpatient clinic visits for prescription of BTFC); much time spent using (frequent outpatient clinic visits for prescription of BTFC); continued opioid use despite knowledge of having physical/psychological problems; activities given up to use (his motivation had gone down while the dose of BTFC had increased); and craving.[14] The 20 μg/hour of transdermal buprenorphine patch (the only available form of buprenorphine in Korea) was applied and was ineffective for controlling the addictive behaviors. Fi-

nally, olanzapine (10 mg/day per os) was given to control the craving behavior and anxiety because, compared with other D2-receptor antagonists, its H1-blockade effect is stronger[15] and there is more evidence to support the role of olanzapine as a treatment for opioid craving.[9–12] Three days later, opioid craving was reduced from five to one on a 5-point Likert scale (It was difficult for me to forget about taking BTFC—1: not at all; 5: very much—not validated to assess the opioid craving). The opioid amount was reduced to MEDD 500 mg/day seven days after the initiation of olanzapine. The pain was well controlled to NRS 1 or 2 without cravings for BTFC and the level of consciousness was alert.

Since 1 week after hospitalization, the patient became depressed and felt his life is worthless. In addition, he complained of insomnia and decrease in appetite. Psychotic features and history of manic/hypomanic episodes were not observed. Under the diagnosis of major depressive disorder, duloxetine 30 mg/day was started and its dose was titrated up to 60 mg/day because it is known to be effective for anxiety and painful physical symptom as well as depression.[16,17] Depressed mood and physical activity then improved over time. However, the patient's craving for BTFC was not reduced at all until he was started on olanzapine.

He was discharged from the hospital four weeks after the initiation of olanzapine, with an average pain NRS of 2 and with MEDD of 520 mg/day. The patient died peacefully three months later due to cancer progression.

Discussion

To our knowledge, this is the first case of an opioid-addicted cancer patient whose craving behavior was successfully controlled by olanzapine. In patients with chronic nonmalignant pain, up to 11.5% of those were reported to have opioid addiction.[18] However, addiction to opioids is uncommon in patients with cancer pain. Although one study indicated that the prevalence of opioid addiction in cancer patients ranged from 0% to 7.7%, it included all problematic opioid uses such as addiction, dependence, improper medication, abuse, and misuse.[4] Schug et al. reported that addiction was a negligible problem, with only 1 observed case out of 550 cancer patients.[19] However, it was also reported that current smokers and alcoholics, as in our patient, were more likely to have a history of illicit drug use than never smokers and nonalcoholics.[20,21] Kwon et al. reported that ~42% of CAGE (cut-down, annoyed, guilty, and eye-opener)-positive patients for alcohol were diagnosed as chemical copers, although this does not necessarily mean that they are addicts.[22]

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnostic criteria, addiction is included in the categories of opioid use disorder.[23] Its severity was classified on the number of diagnostic criteria met by the patient. A minimum of 2 to 3 of the 11 criteria is considered mild, 4 to 5 is moderate, and 6 to 7 indicates severe opioid use disorder. Our patient was classified as severe opioid use disorder by these criteria. However, the DSM-5 diagnostic criteria may not be sufficient to distinguish addiction from other abuse or misuse disorders because physical dependence or pseudoaddiction may easily meet two or more of the criteria. The American Pain Society and the American Society of Addiction Medicine suggest four critical elements of opioid addiction: loss of self-control,

compulsiveness, persistent use despite harm, and craving. Our patient showed all four symptoms necessary for an addiction diagnosis.

Although both psychological and physical dependences on opioids contribute to addiction, their pathophysiological mechanisms are completely different. The mesolimbic system is believed to be an important mechanism in the development of psychological dependence on opioids. When people experience natural rewards, such as food, music, and sex, the neurons of the ventral tegmental area in the midbrain release dopamine into the nucleus accumbens and the prefrontal cortex, which plays a key role in the subjective feelings of pleasure.[24] Opioids induce a rush of dopamines in greater amount than under a normal stimulus and pathologically intercept the brain mechanisms of reward-related learning and memory.[25,26] Considering these pathophysiological mechanisms, olanzapine, a dopamine receptor antagonist, may play a role in managing psychological dependence.[27] The patient in this case was believed to respond to olanzapine through this mechanism. Chronic opioid use leads to neuroplastic changes in the brain of vulnerable individuals with drug-seeking behavior. Short-acting opioids including BTFC are more likely to cause a patient to develop misuse than are other long-acting opioid analgesics.[28] Another study suggested that the pharmacokinetic properties of morphine including the dosage and the rate of administration may affect the abuse liability of the drug.[29]

Physical dependence occurs by changing the cells and synapses in the brain into a hyperadrenergic state through high levels of norepinephrine coming from the locus coeruleus of the anterior pons, which is a physiological response to chronic opioid exposure. If opioids were abruptly stopped, the activated alpha2-adrenergic system dominated by norepinephrine can develop multiple symptoms from adrenergic hyperactivity, including abdominal pain, diarrhea, lacrimation, sweating, chill, yawning, sneezing, general weakness, and insomnia.[30,31] Our patient did not present with physically dependent symptoms.

Pseudoaddiction is defined as an iatrogenic syndrome where a patient displays aberrant behaviors that develop as a result of inadequate pain management. These behaviors are often mislabeled as chemical coping or even addiction. Only after adequate control of pain is achieved do these behaviors resolve and the opioid dose requirements stabilize and even decrease.[32] The patient was initially managed by opioid rotation and by dose escalation of other opioids based on the possibility of pseudoaddiction, but opioid craving was not improved at all. After olanzapine was administered, opioid craving and MEDD were markedly reduced although any anticancer treatment was not performed during this period. These findings may rule out the diagnosis of pseudoaddiction.

Depression is often associated with opioid addiction inpatients.[33] This phenomenon may be explained by the seeking behavior for euphoric agents, such as opioids, in depressed individuals, although an inverse causal relationship may still exist.[34] Our patient showed that the depressed mood was improved by the administration of an antidepressant. However, the patient's craving for BTFC was not reduced at all until he was started on olanzapine. This suggests that the patient's craving behavior may be explained by the opioid addiction rather than by the major depressive disorder.

In conclusion, we provide early evidence that olanzapine may inhibit craving behaviors associated with opioid addic-

tion. There were several limitations to confirm this finding in our patient. Given that the usual therapeutic dose of sublingual buprenorphine to treat opioid addiction is 8 to 16 mg/day,[35] the dose of buprenorphine used in our patient (20 μg/hour of transdermal patch is $\sim$1 mg/day of sublingual type)[36] might be suboptimal. A previous report described that olanzapine was useful as an adjuvant analgesic in cancer patients with anxiety, which may have contributed to the beneficial effect on craving in this patient.[37] In addition, BTFC obsession seen in this patient might have been an attempt to manage his anxiety (chemical coping), which can be controlled by olanzapine. Therefore, further prospective studies are warranted to convince the role of olanzapine as a treatment for opioid addiction.

Author Disclosure Statement

No competing financial interests exist.

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