CASE REPORT

Alleviating Symptoms of Withdrawal from an Opioid

Judith H. Wakim

ABSTRACT

Introduction: Patients who are discharged following surgery on an oral opioid, and who have taken the drug for 2 or more weeks often experience withdrawal symptoms when they try to discontinue the drug.

Case Report: Three weeks after discharge, a 44-year-old female patient decided to reduce her oxycodone (OxyContin®) dosage from 20 mg three times a day to 20 mg two times a day. She experienced severe withdrawal symptoms.

Method: To assist her in withdrawing from the remainder of the drug, a protocol using ondansetron was developed.

Results: After 10 days, the patient was opioid and withdrawal-symptom free.

Conclusion: Use of ondansetron along with tapering of the opioid was safe and effective in preventing further withdrawal symptoms. This case should stimulate research with a larger, more diverse population including those with both short-term and chronic opioid dependence.

Keywords: Ondansetron; Opioid withdrawal syndrome; Oxycodone; OxyContin

J. H. Wakim (✉)
Department 1051, School of Nursing,
The University of Tennessee at Chattanooga,
615 McCallie Avenue, Chattanooga,
TN 37403, USA
e-mail: Judith-Wakim@utc.edu

INTRODUCTION

Patients who have been prescribed an oral opioid postoperatively and who take the drug for 2 or more weeks usually report experiencing withdrawal symptoms when the drug is discontinued. This report describes the case of an individual who was assisted in relieving her physical dependence on oxycodone. It provides an insight into the reason for her surgery, the surgery itself, and her postoperative course. It also reviews medications used, and describes the protocol followed to produce successful results.

CASE REPORT

The patient, a female, was 14 years old when she was diagnosed with scoliosis. She showed no cosmetic effect, nor was there any pressure on her internal organs related to the scoliosis. At age 44, a rib on her left side became noticeably more prominent and measurements showed that she had lost close to two inches in height. She was in good health and had a body mass index below 25. Her only pain medication was an occasional extra-strength acetaminophen. An assessment by an orthopedic surgeon recommended by the Scoliosis Research Society revealed that she had also developed some neuropathy in her left lower limb. A magnetic resonance imaging scan verified thoracic dextroscoliosis and lumbar levoscoliosis with degenerative changes in both areas. Surgery was deemed medically necessary.

Her first surgery was accomplished through a lower abdominal incision. Lumbar vertebra 5 (L5) was replaced by a titanium prosthesis, and a donor bone graft was used to replace the disc. The next day, surgery was performed anteriorly from a left-side incision. A rib was removed, a chest tube was inserted, and discs between T10, T11, T12, and the remaining lumbar vertebrae were temporarily replaced. After surgery, the patient complained of quite a bit of referred pain in her shoulder. She rested on days 3 and 4, but was back in surgery for several hours on day 5. A posterior incision allowed the surgeon to remove the discs from T3 to T9, rotate the spinal column from 85° to 27°, fixate it with rods, screws, and wires, and insert donor bone grafts between all the vertebra. Because the vertebra were scraped to allow fusion with the grafts, the patient required replacement of 14 U of blood.

Postoperatively, the patient had intravenous (i.v.) patient-controlled analgesia (PCA) with morphine. Epidural analgesia was attempted but did not provide any pain relief, so she was maintained on the PCA through day 7. She was then started on 20 mg of controlled-release oxycodone (OxyContin®; Purdue Pharma L.P., Stamford, CT, USA) to be taken orally (p.o.) twice a day, with 5 mg of fast-release oxycodone p.o. as needed for breakthrough pain. On day 9 her controlled-release oxycodone dose was increased to 20 mg at 7:00 a.m., 3:00 p.m., and 11:00 p.m. Fast-release oxycodone 5 mg was continued for breakthrough pain. She was discharged from hospital that afternoon.

A bivalve orthosis (clamshell brace) and two SpinalPak® II Fusion Stimulators (EBI, LLC dba Biomet Spine & Bone Healing Technologies, Parsippany, NJ, USA) were prescribed to stabilize the patient's spine and to stimulate bone growth. The following days were difficult for her. They entailed making her position comfortable, adjusting the clamshell, replacing SpinalPak® batteries, and relieving constipation associated with the surgery and the opioids.

During the first week at home the patient took approximately three oxycodone 5 mg tablets for breakthrough pain, but by the following week she was able to gradually discontinue it. She became more active and was able to climb the stairs to the second floor of the house in spite of some left leg and foot neuropathy. She was anxious to be able to drive her car, but thought that she should not do so while she was still taking the controlled-release oxycodone.

Twenty-five days after receiving her first opioid and almost 3 weeks after discharge from the hospital, the patient discontinued the middle dose of oxycodone, contrary to usual pain management protocols, which recommend partial decreases at each dosage time over many days. She decided to take 20 mg of oxycodone at 8 a.m. and 20 mg at 8 p.m. By 5 p.m. that same day, she became anxious and extremely depressed. She showed the following

signs of withdrawal: crying, cold flashes, piloerection, muscle twitches, tremors, hot flashes, and perspiration. She described symptoms of: abdominal cramps, feeling nauseous and ready to vomit, shaking, and eye twitching. These signs and symptoms lasted over 48 h. She was afraid to reduce the remaining doses of oxycodone and asked for assistance.

METHODS

A review of the literature was conducted through PubMed and yielded many articles dealing with withdrawal from opiates. Keywords used were "oxycontin," "opioid withdrawal," "taper," and after seeing a referral in one article, "ondansetron." A 1986 article from the Johns Hopkins University Hospital [1] described a pilot study of three adult post-addict males who were given different doses of morphine or placebo on 12 mornings followed by 10 mg of naloxone in the afternoons. The study showed that naloxone could precipitate withdrawal signs and symptoms after acute morphine administration similar to those observed after chronic opioid use [1]. That same year, a scientist from the UK reviewed several studies and called attention to the fact that cerebral membranes of both the rat and humans contained sites that were characteristic of 5-hydroxytryptamine3 (5-HT$_3$) receptors. He posited that 5-HT$_3$ antagonists might have the ability to block feelings of reward induced by drug-craving addicts [2].

A Canadian study concluded that 5-HT$_3$ antagonists (ondansetron, and MDL 72222) might reduce some, but not all, signs and symptoms of withdrawal behavior induced by naloxone [3]. Other researchers varied in their conclusions regarding the effectiveness of ondansetron. One study found that it did not reduce the cravings of opiate addicted rodents [4], while another suggested that it could be useful in lowering the rate of relapse [5]. Data reported by a group from Italy confirmed that naloxone precipitated withdrawal signs in morphine-dependent rats, and, that ondansetron prevented several of those signs [6].

In 2009, a research group from Stanford University [7] assessed opioid withdrawal behavior in 18 different strains of mice and in eight human volunteers. The mice were treated with subcutaneous (s.c.) morphine in increasing doses over 4 days, assessed 18 h after the last dose, and then given naloxone s.c. which precipitated varied degrees of withdrawal behavior depending upon the strain of the mice used. The researchers used ondansetron, to determine its effect on the morphine-dependent mice. The ondansetron-treated mice showed significantly decreased naloxone-induced withdrawal behavior [7].

Eight human volunteers, all males, were then recruited, and served as their own controls. Baseline data were obtained by using objective and subjective rating scales [8]. Four volunteers received a 0.9% saline placebo administered intravenously (i.v.) followed by morphine 10 mg/70 kg (i.v.). The remaining four volunteers were pretreated with 8 mg of ondansetron (i.v.), and then received morphine 10 mg/70 kg (i.v.). Two hours after the first set of drugs were administered, all participants received 10 mg/70 kg of naloxone (i.v.) to induce withdrawal symptoms. Seven days later the volunteers were administered the same drugs. The four men who had received placebos in the first experiment received both ondansetron and morphine while the remaining four received the placebo and the morphine. Both objective and subjective signs of withdrawal were assessed and compared to the baseline survey [7].

Evaluation of the effects on all of the human subjects showed that seven of the eight volunteers developed 12 of 13 objective signs of withdrawal. In all seven men, ondansetron significantly reduced all 12 of those signs ($P = 0.0313$). The 16 subjective symptoms, however, were not shown to be significantly lower with the use of ondansetron [7].

Drugs Used

The principle central nervous system effects of opioids are analgesia, euphoria, sedation, respiratory depression, cough suppression, pupil constriction, and temperature changes. Peripheral effects are sometimes seen on the cardiovascular system in patients with hypotension, in the gastrointestinal tract (causing constipation), on the biliary tract, on the functioning of the renal system, on the neuroendocrine system, and in the skin (causing pruritus and sweating). Effects are also seen in the immune system.

People show physical dependence on opioids when they are abruptly stopped. The number and intensity of the signs and symptoms of withdrawal are dependent upon the degree of physical dependence that has developed. Withdrawal signs usually start within 6–10 h after the last dose [9]. Physical dependence should not be confused with tolerance or addiction. Tolerance, a gradual loss of effectiveness, occurs during treatment when large doses of opioid are given close together [10]. Addiction is a relapsing compulsion to obtain and use the drug even after successful withdrawal and in spite of negative effects [9].

Ondansetron is a 5-HT$_3$ antagonist that blocks the action of serotonin. Serotonin is both a powerful stimulant of pain and a strong activator of chemosensitive endings [11]. Serotonin is accepted by 5-HT$_3$ receptors located in the chemoreceptor trigger zone of the brain (area postrema), the vomiting center in the medulla, and in the gastrointestinal tract. It participates in the vomiting reflex, especially in vomiting caused by chemical triggers [11]. Ondansetron is tolerated well and has an excellent safety record. It has proved to be therapeutic in preventing nausea and vomiting related to surgery, chemotherapy, and whole body or abdominal radiation therapy [12]. Ondansetron has been used in the treatment of irritable bowel syndrome, and a Cochrane Collaboration review described its use in relieving acute gastroenteritis in children and adolescents [13].

As for a safe dose in adults and children over 12 years of age, oral ondansetron is given as an 8 mg tablet, 30 min before and again 8 h after an initial dose of chemotherapy or radiation therapy. Then, 8 mg is given every 8–12 h for 1–2 days [14].

Intervention

The patient was assisted in becoming oxycodone free, by tapering the doses of oxycodone and by using ondansetron to make the process more tolerable. Ondansetron had reduced artificially induced withdrawal symptoms for eight male volunteers [7], but the question remained as to whether ondansetron could help alleviate withdrawal in a 44-year-old premenopausal woman who had been on oxycodone for 5 weeks.

The patient obtained prescriptions for oxycodone 10 mg and for oral ondansetron 8 mg. Ondansetron 8 mg was given at 8 a.m. and 8 p.m. every day during the treatment period. It began 48 h before the first dose reduction in oxycodone and continued until 48 h after the last dose of oxycodone. The evening dose of oxycodone was the first to be

Table 1 A 10-day protocol for administering ondansetron and tapering oxycodone to alleviate opioid withdrawal symptoms

Medication	Oxycodone 20 mg	Oxycodone 10 mg	Ondansetron 8 mg
Day and time			
Day 1 8 a.m.	X		X
Day 1 8 p.m.	X		X
Day 2 8 a.m.	X		X
Day 2 8 p.m.	X		X
Day 3 8 a.m.	X		X
Day 3 8 p.m.		X	X
Day 4 8 a.m.	X		X
Day 4 8 p.m.		X	X
Day 5 8 a.m.		X	X
Day 5 8 p.m.		X	X
Day 6 8 a.m.		X	X
Day 6 8 p.m.		X	X
Day 7 8 a.m.		X	X
Day 7 8 p.m.			X
Day 8 8 a.m.		X	X
Day 8 8 p.m.			X
Day 9 8 a.m.			X
Day 9 8 p.m.			X
Day 10 8 a.m.			X
Day 10 8 p.m.			X

reduced to 10 mg. The planned protocol can be seen in Table 1.

Institutional Review Board approval from the University of Tennessee at Chattanooga and written permission from the subject were obtained. Verbal agreement was received from the subject's surgeon to allow dissemination of information related to her surgery and postoperative recovery.

RESULTS

During the 10 days of the weaning process, the patient neither exhibited nor voiced any symptoms of withdrawal from the opioid. In fact, she expressed fear of becoming dependent on the ondansetron because of the feeling of well-being it gave her. She was reassured that the ondansetron acted on different receptors in the body than did the opioids, and that her prior withdrawal symptoms had been normal for what she had been through, and not symptoms of addiction. This reassurance stemmed from knowing that antidepressants, which (like ondansetron) block serotonin uptake, have not been shown to cause addiction even after prolonged use [9].

At the conclusion of the protocol, the patient disposed of the remaining oxycodone according to the Food and Drug Administration (FDA) guidelines. She was featured as a model patient after a month of visits to a physical therapy group. She continues to walk daily on her treadmill and enjoys advanced hula-hoop exercises on the Wii[TM] (Nintendo[®], Redmond, WA, USA). Some may argue that the same effect could have been achieved by simply tapering the dose of opioids at a slower rate and over a longer period of time. For instance, the patient could have been advised to remove only 10 mg of the middle dose of oxycodone, wait 4 days and remove 10 mg of the evening dose, then wait the same number of days and remove 10 mg of the morning dose. Since oxycodone does not come in smaller doses than 10 mg, and since controlled release could not be effectively achieved by cutting the tablet in half (5 mg), the patient may have had to endure some withdrawal symptoms as the remaining doses were discontinued over a 30-day period.

CONCLUSION

Reducing dependence on oxycodone is a big hurdle for many people who have had orthopedic or other major surgery. Statistics are already showing increased percentages of knee, hip, shoulder, and back surgery in people born between 1946 and 1964 ("baby boomers"),

an age group that has engaged in more active sports than any previous generation. As these people grow older, it can be postulated that the incidence of oxycodone dependence will increase. Military personnel are also seeing an increase in opiate dependence [15]. To alleviate or prevent the signs and symptoms of opioid withdrawal and to combat the possibility of some of these people becoming addicts, it would be wise to conduct randomized controlled trials on both males and females, young and old, with both acute and chronic opioid dependence (not associated with a terminal condition), to determine the effects of ondansetron given prior to beginning tapering off of the opioid.

ACKNOWLEDGMENTS

REFERENCES

1. Bickel WK, Stitzer ML, Wazlavwk MA, Liebson IA. Naloxone-precipitated withdrawal in humans after acute morphine administration. NIDA Res Monogr. 1986;67:349–54.

2. Tricklebank MD. Interactions between dopamine and 5-HT$_3$ receptors suggest new treatments for psychosis and drug addiction. Trends Pharmacol Sci. 1989;10:127–9.

3. Higgins GA, Nguyen P, Joharchi N, Sellers EM. Effects of 5-HT$_3$ receptor antagonists on behavioural measures of naloxone-precipitated opioid withdrawal. Psychopharmacology. 1991;105:322–8.

4. Sell LA, Cowen PJ, Robson PJ. Odansetron and opiate craving. A novel pharmacological approach to addiction. Br J Psychiatry. 1995;166:511–4.

5. Hui SC, Sevilla EL, Ogle CW. Prevention by the 5-HT$_3$ receptor antagonist, ondansetron, of morphine-dependence and tolerance in the rat. Br J Pharmacol. 1966;118:1044–50.

6. Pinelli A, Trivulzio S, Tomasoni L. Effects of ondansetron administration on opioid withdrawal syndrome observed in rats. Eur J Pharmacol. 1997;340:111–9.

7. Chu LF, Liang D, Li X, et al. From mouse to man: the 5-HT3 receptor modulates physical dependence on opioid narcotics. Pharmacogenet Geonomics. 2009;19:193–205.

8. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13:293–308.

9. Lüscher C. Drugs of abuse. In: Katzung BG, Masters SB, Trevor J, editors. Basic and clinical pharmacology. 11th ed. New York: McGraw-Hill; 2009. p. 553–68.

10. Schumacher MA, Basbaun AT, Way W. Opioid analgesics and antagonists. In: Katzung BG, Masters SB, Trevor J, editors. Basic and clinical pharmacology. 11th ed. New York: McGraw-Hill; 2009. p. 531–52.

11. Katzung BG. Histamine, serotonin, & the ergot alkaloids. In: Katzung BG, Masters SB, Trevor J, editors. Basic and clinical pharmacology. 11th ed. New York: McGraw-Hill; 2009. p. 271–92.

12. McQuaid KR. Drugs used in the treatment of gastrointestinal diseases. In: Katzung BG, Masters SB, Trevor J, editors. Basic and clinical pharmacology. 11th ed. New York: McGraw-Hill; 2009. p. 1067–101.

13. Alashimi D, Alhashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Cochrane Database Syst Rev. 2009;(2):CD005506.

14. 2012 Nurse's Drug Handbook. 11th ed. Boston: Jones and Bartlett Learning; 2012:793–4.

15. Zoroya G. The general's drug problem. USA Today. January 27, 2011:1A–2A. Available at: http://www.usatoday.com/news/military/2011-01-27-1Adruggeneral27_CV_N.htm. Last accessed August 25, 2012.