Palliative and Supportive Care

cambridge.org/pax

Naldemedine-induced opioid withdrawal syndrome with severe psychiatric symptoms in an advanced cervical cancer patient without brain metastasis

Mayumi Ishida, C.P., PH.D.[1], Mie Hiraoka, C.N.[2], Ayako Yaguchi, PH.D.[3], Koji Sugano, M.D., PH.D.[4], Nasako Adachi, C.N.S.[2], Tomoko Itoga, M.D., PH.D.[5], Tomohito Ishiguro, M.D., PH.D.[5] and Hideki Onishi, M.D., PH.D.[1]

[1]Departments of Psycho-oncology, Saitama Medical University International Medical Center, Saitama, Japan; [2]Department of Nursing, Koshigaya Municipal Hospital, Saitama, Japan; [3]Department of Pharmacy, Koshigaya Municipal Hospital, Saitama, Japan; [4]Division of Respiratory Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan and [5]Department of Obstetrics and Gynecology, Koshigaya Municipal Hospital, Saitama, Japan

Case Report

Cite this article: Ishida M, Hiraoka M, Yaguchi A, Sugano K, Adachi N, Itoga T, Ishiguro T, Onishi H (2022). Naldemedine-induced opioid withdrawal syndrome with severe psychiatric symptoms in an advanced cervical cancer patient without brain metastasis. *Palliative and Supportive Care* **20**, 445–447. https://doi.org/10.1017/S1478951521001917

Received: 7 October 2021
Revised: 20 November 2021
Accepted: 4 December 2021

Key words:
Cancer; Case report; Delirium; Naldemedine; Opioid withdrawal syndrome

Author for correspondence:
Mayumi Ishida,
Department of Psycho-oncology,
Saitama Medical University International Medical Center, 1397-1 Yamane,
Hidaka City, Saitama 350-1298, Japan.
E-mail: mayumi_i@saitama-med.ac.jp

Abstract

Objective. Naldemedine, an oral peripheral μ-opioid receptor antagonist, was developed for the treatment of constipation, a side effect of opioid use. Naldemedine is not generally recognized as causing opioid withdrawal in which associated symptoms affecting the central nervous system.

Method. From the series of cancer patients undergoing symptom management, we report a case treated with naldemedine for constipation in relation to the use of opioids for cancer pain and who displayed severe psychological symptoms associated with withdrawal immediately after the use of naldemedine.

Results. The patient was a 36-year-old woman diagnosed with cervical cancer Stage IIB, PS3. When the patient, who was using oxycodone hydrochloride hydrate (80 mg/day) for ileal pain, was started on naldemedine for constipation, she complained of sweating after just 5 min and hallucinations after 1 h. The patient also displayed physical/behavioral abnormalities such as diarrhea and hyperactivity, and psychological abnormalities such as aggression toward staff.

Despite the psychiatric symptoms worsening over time, there were no abnormalities in terms of blood biochemical data, and no brain metastasis was observed on MRI. Based on the Clinical Opiate Withdrawal Scale, these symptoms were judged to indicate opioid withdrawal. Naldemedine was discontinued due to naldemedine-related opioid withdrawal syndrome and, thereafter, the psychiatric symptoms diminished, with no recurrence of similar symptoms observed to date.

Significance of results. If mental and behavioral abnormalities occur in patients receiving naldemedine, it is necessary to consider the possibility of opioid withdrawal syndrome as a differential diagnosis.

Introduction

Constipation is one of side effects of opioid use. This is known as opioid-induced constipation (OIC) and occurs in 80% of patients using opioids, leading to a decrease in patient quality of life (Mesía et al., 2019). Conventional laxatives have been used to treat OIC; however, naldemedine, an oral peripheral μ-opioid receptor antagonist, has recently been developed. The drug improves OIC by binding to opioid receptors in the gastrointestinal tract and antagonizing opioids. In addition, as this drug does not cross the blood–brain barrier, it does not affect the analgesic effects, and opioid withdrawal-related CNS symptoms do not appear (Katakami et al., 2017; Webster et al., 2018; Coluzzi et al., 2020). The same is true for patients with blood–brain barrier disruption (Osaka et al., 2019). Furthermore, there has been no report to date of opioid withdrawal accompanied by severe psychiatric symptoms after the administration of naldemedine.

Here, we report a case of constipation in a patient who used opioids for cancer pain, and who experienced opioid withdrawal symptoms with severe psychiatric symptoms immediately after the administration of naldemedine.

Case report

The patient was a 36-year-old female diagnosed with Stage IIB cervical cancer and who had undergone radical hysterectomy 16 months prior to her referral to us, followed by four courses of Taxotere and Cyclophosphamide (TC) therapy. However, the disease recurred and radiation

CAMBRIDGE UNIVERSITY PRESS

therapy was performed. Four months prior to her referral, metastasis appeared in the rectum, and Irinotecan (CPT-11) + Nedaplatin (NDP) was started. A month later, she underwent emergency hospitalization for fever and lower abdominal pain during the third course of CPT-11 + NDP. An ileal tube was inserted on diagnosis of intestinal obstruction; however, as the symptoms did not improve, small intestine-ascending colon bypass surgery was performed. Oxycodone hydrochloride hydrate (10 mg) was started for pain relief, with the dosage gradually increased to 80 mg. The ileus was temporarily released after surgery, but constipation due to infiltration of the tumor to the rectum recurred thereafter. As abdominal pain was exacerbated by a large intestine-stimulating laxative, no improvement was observed even after the start of magnesium oxide administration at 750 mg/day, so the administration of naldemedine (0.2 mg) was started. The patient's performance status (PS) was 3.

The patient was administered naldemedine orally at 10 pm, and sweating appeared 5 min later. At around 30 min thereafter, the patient began complaining to nurse while crying. An hour later, she visited the nurse station saying, "Did you just use a smoke spray? Are there cockroaches?" and "Small insects are swarming into this IV bag." After 3 h, diarrhea appeared, with the patient often leaving her room to visit the bathroom because of frequent episodes of diarrhea. She also complained of insomnia.

The next morning, the patient was unable to settle, often opening and closing the curtains on the window and changing the position of the bed and her luggage in the hospital room. She was tearful and excitable, and she continued to complain emotionally to the staff using unusual and inappropriate language. She also sweated profusely and complained that "the room is hot."

As the above psychiatric symptoms were marked and worsened over time, the ward staff referred the patient to the palliative care team, which included a psychologist, for consultation and a medical examination was performed in the ward. At the time of the examination, she was friendly to the psychologist and said with a smile, "I'm talking too much today," but gradually she became more contrary, and, finally, she grew excited and asked in an aggressive tone, "What should I do when you ask that?" Her conversation was mostly one-sided, and she easily deviated from the topic at hand. Gradually, she lost the ability to concentrate on the interview, rubbing the desk at the nurse station relentlessly, crying and laughing frequently, wiping sweat all over her face with a handkerchief and continuing to talk in an aggressive tone. In reference to the situation, the patient said that, "Yesterday, I suddenly became like this after the medicine was changed! I couldn't move from bed at all! You're surprised by this!"

Thereafter, when she was examined by his doctor and received an explanation of her condition, she was aggressive throughout and displayed an inappropriate attitude, such as sitting on her knees on the sofa and arrogantly turning her back. Fever (37.8° C), tachycardia (160 beats/min), sweating, tremors, lacrimation, runny nose, and disorientation based on misidentification of the date were observed on medical examination. There were no abnormalities in the blood biochemical data, and no brain metastasis was observed on MRI. Pain was controlled by continuous intravenous administration of oxycodone hydrochloride hydrate (80 mg/day) and oral acetaminophen, and there were no complaints of pain from after the oral administration of naldemedine to the time of following morning's interview, but the patient did display hyperactivity. The patient was also administered acetaminophen 2,000 mg, meropenem hydrate 3,000 mg, and magnesium oxide 750 mg. However, no drug acting as a permeability glycoprotein (P-gp) inhibitor was administered.

From the above, opioid withdrawal was considered as a possible diagnosis. The patient showed a very high score of 30/46 points on the Clinical Opiate Withdrawal Scale (COWS; Wesson and Ling, 2003), and the opioid withdrawal symptoms were judged to be moderately severe (a score > 36 is considered severe withdrawal). Her COWS subset scores were as follows: Resting pulse rate 4, Sweating 4, Restlessness 5, Bone or joint aches 1, Runny nose or tearing 4, GI Upset 4, Tremor 4, Yawning 0, and Anxiety or Irritability 4. Pupil size and Gooseflesh skin could not be fully confirmed as the patient strongly refused examination.

In response to this series of symptoms, naldemedine was discontinued due to naldemedine-related opioid withdrawal syndrome and opioid withdrawal delirium. About one day after discontinuation of naldemedine administration, the aggressive attitude toward staff gradually disappeared, and it became possible for her to remain calm on her bed in the hospital room. Her symptoms such as sweating and tachycardia gradually improved, and although she remained somewhat talkative, she said with a smile, "I feel like I'm talking so much because of the medicine," and returned toward her previous condition. Thereafter, her psychiatric symptoms further subsided, and no similar symptoms have appeared since.

The patient was employed by a company, had no memory of mental illness such as alcoholism or drug addiction, and had good relationships with friends and family.

Discussion

The diagnostic basis for opioid withdrawal by Naldemedine (American Psychiatric Association, 2013) in this case was the sudden appearance of psychiatric and physical symptoms immediately after the administration of naldemedine to the patient receiving opioids. In addition, after discontinuation of naldemedine, the symptoms improved and no similar symptoms were later observed. Furthermore, no blood biochemical data or imaging findings that could explain the condition at this time were observed, leading to a definitive diagnosis. The main characteristic of this case was that the patient exhibited extremely severe psychiatric symptoms. Immediately after the administration of naldemedine, the psychiatric symptoms rapidly increased, and the patient began to show anger and an aggressive attitude toward the staff. In addition, behavioral changes were noted, such as hyperactivity, which presented as restlessness in the ward.

To the best of our knowledge, there is only one report of opioid withdrawal syndrome due to naldemedine administration (Ishii et al., 2020), and although moderate physical symptoms occur 1 h after administration, it is not accompanied by severe psychiatric symptoms such as those observed in this case. It should be kept in mind that, as in this case, there may be some cases which mainly present with severe psychiatric symptoms.

In this case, opioid withdrawal syndrome was considered on the basis of severe psychiatric symptoms that appeared after the administration of naldemedine; however, without careful observation, delirium, a psychiatric symptom common in cancer patients, may be diagnosed and appropriate treatment for opioid withdrawal may not be initiated. Naldemedine and opioids are often used in combination for patients with advanced cancer. If such patients experience rapid worsening of psychiatric symptoms, it

https://doi.org/10.1017/S1478951521001917 Published online by Cambridge University Press

may be necessary to differentially add opioid withdrawal syndrome due to naldemedine administration as the cause.

Naldemedine is a known substrate for P-gp. A study using multidrug resistance protein 1a/b knockout mice revealed that the administration of a P-gp inhibitor increased the distribution of naldemedine in the brain by about four times that in wild-type mice, although the concentration in the brain itself was very low. The reason for the low concentration of naldemedine in the brain is that its ability to cross the blood–brain barrier is limited, and it is thought that the action of the P-gp inhibitor is minimal (Watari et al., 2019). No P-gp inhibitor was administered in this case, and the cause of onset of withdrawal will be elucidated through future research.

As a limitation, in this case, the absence of brain metastasis was confirmed by MRI before and after the onset of opioid withdrawal symptoms, but it was not visually confirmed, and it was not a therapeutic problem even in the subsequent course. However, there is a level of brain metastasis that cannot be visually confirmed, and it is possible that naldemedine had crossed the blood–brain barrier. From this, it can be said that caution is required in relation to opioid withdrawal induced by naldemedine regardless of the presence or absence of brain metastasis.

Conclusion

Immediately after the administration of naldemedine, our patient experienced opioid withdrawal syndrome with severe psychiatric symptoms. If mental and behavioral abnormalities occur in patients receiving naldemedine, it is necessary to consider the possibility of opioid withdrawal syndrome as a differential diagnosis.

Conflicts of interest. The authors declare that they have no conflict of interest.

References

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Publishing.

Coluzzi F, Scerpa MS and Pergolizzi J (2020) Naldemedine: A new option for OIBD. *Journal of Pain Research* **13**, 1209–1222.

Ishii K, Yamashita H, Yamaguchi M, *et al.* (2020) Naldemedine-induced opioid withdrawal syndrome in a patient with breast cancer without brain metastasis. *Internal Medicine* **59**(2), 293–296.

Katakami N, Harada T, Murata T, *et al.* (2017) Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. *Journal of Clinical Oncology* **35**(34), 3859–3866.

Mesía R, Virizuela Echaburu JA, Gómez J, *et al.* (2019) Opioid-induced constipation in oncological patients: New strategies of management. *Current Treatment Options in Oncology* **20**(12), 91.

Osaka I, Ishiki H, Yokota T, *et al.* (2019) Safety and efficacy of naldemedine in cancer patients with opioid-induced constipation: A pooled, subgroup analysis of two randomised controlled studies. *ESMO Open* **4**(4), e000527.

Watari R, Matsuda A, Ohnishi S, *et al.* (2019) Minimal contribution of P-gp on the low brain distribution of naldemedine, a peripherally acting μ-opioid receptor antagonist. *Drug Metabolism and Pharmacokinetics* **34**(2), 126–133.

Webster LR, Nalamachu S, Morlion B, *et al.* (2018) Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: A randomized, double-blind, placebo-controlled phase 3 study. *Pain* **159**(5), 987–994.

Wesson DR and Ling W (2003) The clinical opiate withdrawal scale (COWS). *Journal of Psychoactive Drugs* **35**(2), 253–259.

https://doi.org/10.1017/S1478951521001917 Published online by Cambridge University Press