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Opioid withdrawal syndrome developing after long-term administration of naldemedine

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Case Report

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Abstract

Objective. One of the side effects of opioid administration is opioid-induced constipation (OIC). To address this side effect, the oral peripheral μ opioid receptor antagonist naldemedine was developed. As this drug does not cross the blood–brain barrier, it is thought that it does not lead to opioid withdrawal syndrome (OWS) with central nervous system symptoms.
Methods. Here, we report a cancer patient who presented with symptoms centered round anxiety and irritation 4 months after administration of naldemedine for OIC and who was diagnosed with OWS after close investigation.
Results. The patient was a 65-year-old female who had surgery for stage IB endometrial cancer 4 years previously, but experienced recurrence involving the pelvis 2 years later. Medical narcotics were used to control pain, but naldemedine was started to control subsequent constipation. When naldemedine-related OWS was suspected and the administration of naldemedine discontinued, the above symptoms disappeared within two days, and no recurrence was observed thereafter.
Significance of the results. For patients receiving naldemedine, it is necessary to consider the possibility of OWS regardless of the period of administration in order to maintain patient quality of life.

Introduction

One of the side effects of opioid administration is opioid-induced constipation (OIC), which is reported to occur in 80% of opioid-treated patients and is associated with reduced quality of life (QOL) (Mesía et al., 2019). To address this side effect, the oral peripheral μ opioid receptor antagonist naldemedine was developed. This drug improves OIC by competitively binding to opioid receptors present in the gastrointestinal tract. In addition, as this drug has a large molecular weight and does not cross the blood–brain barrier, it does not affect the central analgesic effect, and it is thought not to lead to opioid withdrawal syndrome (OWS) with central nervous system symptoms (Katakami et al., 2017; Coluzzi et al., 2020), with similar results obtained for a study on its long-term use (Webster et al., 2018).

However, when naldemedine was administered to patients with OIC, cases of OWS were reported shortly after administration (Ishii et al., 2020; Ishida et al., 2021). Despite this, no findings regarding OWS in relation to long-term administration have been obtained.

Here, we report a cancer patient who presented with symptoms centered on anxiety and irritation 4 months after administration of naldemedine for OIC and who was diagnosed with OWS on the basis of close investigation.

Case report

The patient was a 65-year-old woman who had undergone surgery for stage IB endometrial cancer 4 years previously. She complained of constipation and recurrent tumors were subsequently found in the pelvis by CT 2 years after surgery. She then received extra beam radiotherapy followed by chemotherapy with docetaxel and carboplatin (Nomura et al., 2011). However, a disease progression was observed after 11 cycles of chemotherapy. A mass was also found in the mammary gland, which was diagnosed as breast cancer during chemotherapy. In addition, rectal and vaginal fistulas formed due to tumor infiltration, and the patient required to undergo colostomy. Due to overlapping events described above, the patient became depressive and there was a request for consultation at the Department of Psycho-Oncology.

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At the first visit, she was found to suffer anxiety about her condition and the artificial anal sphincter, and to feel guilty that she was burdening her family. She had no history of alcohol or drug addiction. She had a calm character and enjoyed strong interpersonal and family relationships. Her psychiatric features fulfilled the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria (American Psychiatric Association, 2013) for adjustment disorder with mixed anxiety and depressed mood.

She received individual and group psychotherapy for patients with recurrent cancer, and her anxiety and guilt were alleviated.

Five months after her initial visit to the Department of Psycho-Oncology, anal pain caused by a pelvic tumor appeared, so the administration of oxycontin (10 mg) was started; however, as the anal pain was not well controlled, tapentadol was added from the 7th month, and naldemedine (0.2 mg) was added as a measure against constipation. In the 8th month, methadone was added, which considerably reduced the pain and improved her level of daily living.

Eleven months after the initial psychiatric examination, she complained that she was more anxious and restless, and that it was difficult for her to wait patiently at the time of her outpatient visits. In addition, symptoms such as fanning of the face due to sudden sweating were also observed. No diarrhea or pain was noted.

At the time, she was receiving tapentadol hydrochloride (200 mg), acetaminophen (1,000 mg), naldemedine (0.2 mg), methadone hydrochloride (30 mg), benfotiamine (100 mg), pyridoxine hydrochloride (100 mg), and cyanocobalamin (1,000 μg).

At first glance, the symptoms were akathisia-like due to the anxiety and restlessness, but she was not receiving any antipsychotic drugs likely to induce akathisia. She had been receiving naldemedine for 4 months and anxiety and sweating were prominent. OWS was suspected based on previous reports of OWS due to naldemedine (Ishii et al., 2020; Ishida et al., 2021) and it was decided to discontinue naldemedine treatment and follow-up.

At her outpatient visit one week later, all the above symptoms had disappeared. According to the patient, she had symptoms such as restlessness being unable to do anything, not being able to wait patiently at her outpatient consultation, and being unable to concentrate when listening to the doctor in charge the previous, but these symptoms disappeared one or two days after the discontinuation of naldemedine.

Her score on the Clinical Opiate Withdrawal Scale (COWS) (Wesson and Ling, 2003), improved from 8 points (mild withdrawal) to 0 points (Table 1).

No similar symptoms have recurred during the 6 months since.

Based on the above, the patient was diagnosed with OWS due to naldemedine.

Table 1. The Clinical Opiate Withdrawal Scale (COWS) before and after discontinuation of naldemedine

Item	Before discontinuation	One week after discontinuation
Resting pulse rate	NA	NA
GI Upset: Over last 1/2 h	0	0
Sweating: Over past 1/2 h not accounted for by room temperature or patient activety	3	0
Tremor: Observation of outstretched hands	0	0
Restlessness: Observation during assessment	3	0
Yawning: Observation during assessment	0	0
Pupil Size	NA	NA
Anxiety or Irritability	2	0
Bone or Joint aches	0	0
Gooseflesh Skin	0	0
Runny Nose or Tearing	0	0
Total	8	0

Score: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; more than 36 = severe withdrawal.
NA, Not Available.

Discussion

Four months after the start of naldemedine treatment for OIC, the patient experienced OWS, with anxiety and irritability as the main symptoms. These findings are very useful in relation to the side effects of naldemedine administration and in the differentiation of anxiety and irritability, which are commonly observed psychological symptoms in cancer patients.

In this case, the patient complained that she was restless and that it was difficult to wait patiently for outpatient consultations, so we considered akathisia as a differential diagnosis (Kawanishi et al., 2007). However, the patient was not receiving any psychotropic drugs that might have caused the onset of akathisia, and this diagnosis was contradicted by her sweating, which is rare in akathisia.

A feature of this case was the appearance of withdrawal syndrome 4 months after the start of naldemedine administration. The cases of naldemedine-induced withdrawal syndrome reported to date differed significantly in that the onset of symptoms was observed within 1 h after administration (Ishii et al., 2020; Ishida et al., 2021). The cause of the appearance of OWS at 4 months after administration of naldemedine is unknown, and future research is required to clarify this.

One limitation to this case report is that no head CT was performed. However, no clinical symptoms suggestive of brain metastasis were observed, and this was true even after 6-months of administration. In addition, no detailed blood tests other than for liver function and renal function were performed. In addition, the resting pulse rate and pupil size required for COWS evaluation were not measured at the time of examination.

Conclusion

We experienced a case of OWS that developed 4 months after the start of naldemedine administration. For patients receiving naldemedine, it is necessary to consider the possibility of OWS regardless of the period of administration in order to maintain patient QOL.

References

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

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

Ishida M, Hiraoka M, Yaguchi A, *et al.* (2021) Naldemedine-induced opioid withdrawal syndrome with severe psychiatric symptoms in an advanced cervical cancer patient without brain metastasis. *Palliative & Supportive Care*, 1–3. doi: 10.1017/S1478951521001917.

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.

Kawanishi C, Onishi H, Kato D, *et al.* (2007) Unexpectedly high prevalence of akathisia in cancer patients. *Palliative & Supportive Care* **5**(4), 351–354.

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.

Nomura H, Aoki D, Takahashi F, *et al.* (2011) Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: A Japanese Gynecologic Oncology Group Study (JGOG2041). *Annals of Oncology* **22**(3), 636–642.

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/S147895152200044X Published online by Cambridge University Press