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A Case of Esophagogastric Junction Cancer Treated with Pain Control by Administering Methadone Tablets Through a Gastrostomy

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Abstract

Introduction: Methadone is used to treat intractable cancer pain when other opioid analgesics are ineffective. Methadone tablets may be difficult to administer in cases of gastrointestinal passage obstruction. However, changing the route of methadone tablet administration is possible.

Case Description: The patient, diagnosed with esophagogastric junction cancer with multiple metastases, continued to receive methadone tablets even after not being longer able to take oral medication.

Method: Methadone tablets were administered using a simple suspension method via gastrostomy. We measured the respiratory rate during sleep daily. We also measured weekly QTc values using a 12-lead electrocardiogram and methadone blood concentration periodically. No side effects were observed.

Conclusion: Using a simple suspension method to administer methadone is a safe pain management method when accompanied by careful monitoring. To date, no study has examined the tube administration safety of methadone tablets. Thus, this case report is of important clinical significance.

Keywords: methadone; cancer pain; esophagogastric junction cancer; simple suspension method

Introduction

Methadone is an opioid analgesic with excellent analgesic effects that not only acts on μ opioid receptors but also blocks *N*-methyl-D-aspartate receptors.[1] It is used to treat intractable cancer pain when other opioid analgesics are ineffective. It is only available in tablet form in Japan, which is challenging for gastrointestinal obstruction cases. Thus, some patients switch to other opioid analgesics.[2] However, no reports have examined the continued administration of methadone tablets in cases where oral administration was difficult. Furthermore, a clear conversion ratio with other opioid analgesics has not been established, the blood concentration half-life of the drug is very long, significant individual differences exist,[3] and severe side effects such as QT interval prolongation and respiratory depression have been observed.[4-6] Therefore, consideration is required for the safe use of methadone tablets.

We encountered a case in which methadone tablets were administered using a simple suspension method to a patient with intractable cancer pain who had difficulty eating due to advanced esophagogastric junction cancer and underwent

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gastrostomy. The simple suspension method is a method of administering tablets and capsules developed by Kurata et al.[7] Although this method is limited in the number of drugs that can be used, it enables the administration of oral drugs through a tube, even for patients who have difficulty taking them orally. We performed safe pain management through careful monitoring. Therefore, this case will be helpful in considering pain control management in patients with similar pathologies. Written informed consent was obtained from the patient, and the study complied with patient privacy protection (Surgery-related Academic Society Council) guidelines for medical papers, including case reports and presentations, at academic meetings. The study obtained approval from the Institutional Review Board of Tohoku Medical and Pharmaceutical University Hospital (approval number: 2022-2-002).

Case Description

The patient was a man in his 60s who presented with complaints of tightness in his chest while eating and a lump on his right clavicle. Following testing, he was diagnosed with cancer of the esophagogastric junction with multiple metastases (lymph nodes, liver, and bones). Chemotherapy (S-1 + CDDP, 4 courses; RAM + PTX, 3 courses; CPT-11, 2 courses) was administered for treating esophagogastric junction cancer; however, oral intake was difficult due to narrowing of the gastrointestinal tract owing to tumor invasion. Therefore, the patient was admitted to the hospital for a gastrostomy. The patient developed significant lower back pain (numerical rating scale [NRS] score = 6/10), which was thought to be due to sacral metastasis.

Subsequently, the palliative care team initiated pain control. Initially, 75 mg/day of tramadol was administered via gastrostomy. The morphine injection was changed to 10 mg/day for dosage adjustment, with the assumption that the patient would be switched to morphine sustained-release fine granules. The morphine injection dosage was increased to 50 mg/day according to the pain situation, and radiotherapy (30 Gy/10 fr) was administered simultaneously, resulting in the improvement of the lower back pain (NRS = 3/10). However, shoulder joint pain (NRS = 5/10) due to newly appeared metastasis to the right humerus remained unchanged even after increasing the morphine injection dosage; moreover, the analgesic effect of the rescue doses was poor. Therefore, we suspected intractable cancer pain and considered switching to methadone tablets.

Because 50 mg/day of morphine injection is equivalent to 100 mg/day of oral morphine, the methadone tablet dosage after switching was 15 mg/day (5 mg/dose, every eight hours). The morphine injection was gradually tapered off while monitoring pain and drowsiness. For rescue doses during the tapering of morphine injections, we administered a 4.1 mg/dose of morphine injection rapidly, with a guideline of 1/24 of the daily dose of morphine injections. We administered oxycodone powder through gastrostomy for rescue doses after morphine injections were completed.

We decided to titrate the oxycodone powder starting at 15 mg/dose using the guideline of 1/6 to 1/8 of the daily dose of morphine injections converted to oral morphine. Furthermore, we administered the methadone tablets through gastrostomy after making suspensions in warm water (55°C) using the simple suspension method.[7] The respiratory rate during sleep was measured daily (Fig. 1A), the QTc value was measured using a 12-lead electrocardiogram weekly (Fig. 1B), and the methadone blood concentration was measured periodically (Days 1 [start date], 5, 7, 10, and 14) (Fig. 2A).

On Day 1, the dosage of methadone tablets was 15 mg/day, with the morphine injection dosage being reduced to 40 mg/day. Rescue doses were mainly used to treat pain from the upper arm and neck to both scapulae (NRS = 2–4/10). As no increase in pain was observed (NRS = 1–4/10), the morphine injection dosage was reduced to 30 mg/day on Day 2. The pain remained the same thereafter; consequently, the morphine injection dosage was reduced to 20 and 10 mg/day on Days 3 and 4, respectively. On Day 4, palliative radiotherapy (30 Gy/10 fr) was initiated for the right humeral metastasis. Although no pain increase was observed on Day 5, the patient complained of sleepiness; therefore, the morphine injection was maintained at 10 mg/day and discontinued on Day 7. The methadone tablet dosage was increased to 20 mg/day (10 mg/dose every 12 hours) on Day 10 because of persistent pain with an NRS of = 2–4/10 after discontinuing the morphine injection.

Moreover, pain in the right shoulder (NRS = 4/10) was judged to be more likely to originate from the right supraclavicular lymph node metastasis than from the right humeral bone metastasis. Therefore, palliative radiotherapy (20 Gy/5 fr) was initiated for the right supraclavicular lymph node from Day 10. Although a temporary increase in back pain (NRS = 7/10) was observed on Day 11, the pain remained generally the same. However, the disease progressed rapidly, and delirium symptoms gradually worsened as the general condition of the patient worsened. On Day 18, owing to acute exacerbation of the underlying disease, a sudden drop in blood

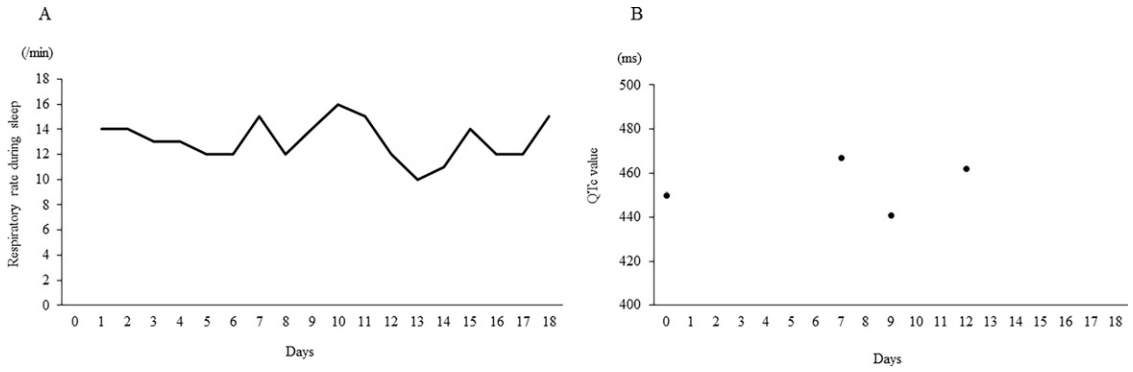

FIG. 1. **(A)** Respiratory rate changes and **(B)** QTc value changes.

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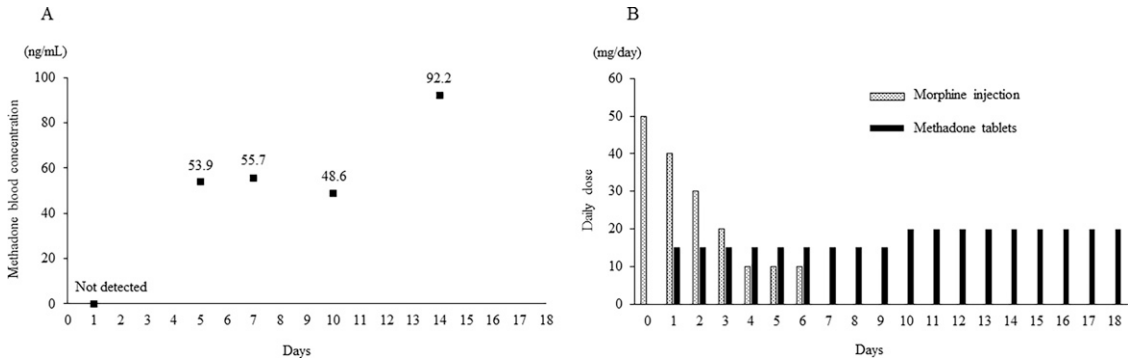

FIG. 2. **(A)** Methadone blood concentration changes and **(B)** dose transition of narcotic analgesics.

pressure and consciousness due to bleeding from the gastrostomy was observed, and the patient died. Figure 2B illustrates the opioid analgesic dose changes before and after starting methadone tablets, while Figure 3 illustrates the NRS changes and number of rescue doses.

Discussion

We evaluated the feasibility of administering methadone tablets using a simple suspension method[7] based on the dissolution properties and stability of the drug under various conditions. The dissolution properties of Methapain® tablets were investigated using the rotating basket method using 500 mL of water as the test solution at 100 rotations per minutes; the dissolution rate was 93.4% to 102.2% for 5 mg tablets and 94.8% to 102.3% for 10 mg tablets. Furthermore, long-term storage tests and stress testing demonstrated no changes due to heat. Thus, methadone tablets have good dissolution properties, are less affected by heat, and can be administered via a simple suspension method. Similarly, the stress testing results demonstrated an increase in analog levels, so leaving the methadone tablets suspended for a long time, even under diffused room light was considered undesirable; therefore, the drug was administered immediately. To detect the early side effects caused by a sudden increase in the blood concentration of the drug after administration, we checked the breathing rate during sleep daily, 12-lead electrocardiogram to verify the QTc weekly, and methadone blood concentration periodically.

Regarding the influence of tube administration of methadone tablets as a simple suspension method on clinical efficacy, no significant changes were observed in the maximum and minimum NRS values, even after introducing methadone. The patient no longer awoke at night due to pain, and the rescue dose frequency decreased; therefore, it was considered clinically effective. For safety, we monitored QT interval prolongation[8] and respiratory depression, which have been reported to correlate positively with methadone blood concentrations. No abnormalities that could be considered side effects were observed in the QTc value or breathing rate during sleep. Therefore, no side effects were caused by the change in administration route within the scope of monitoring (Fig. 1). We also examined the changes in methadone blood concentrations, which have not been reported during simple suspension administration. The methadone blood concentration increased over time in the range of 50–100 μg/mL until Day 7, which was in analogy to the transition observed in the 15 mg/day methadone tablet group reported by Nakamura et al.[9] (Fig. 2A). As no other data are available on oral methadone administration, making a direct comparison is difficult. However, we concluded that no significant change in blood concentration occurred owing to the administration of methadone tablets using the simple suspension method. In addition,

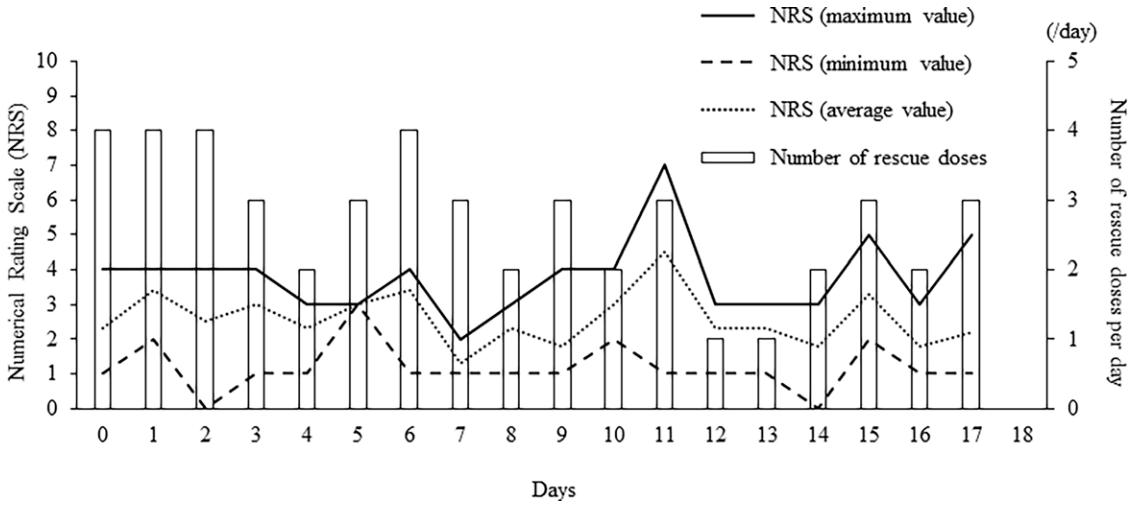

FIG. 3. Rescue dose changes and numerical rating scale (NRS).

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when the methadone blood concentration decreased on Day 10, which is thought to be due to the induction of auto metabolism of methadone, an increase in NRS and the number of rescue doses was observed. However, on Day 14, when the dosage was increased to 20 mg/day of methadone tablets accompanied by an increase in the methadone blood concentration, a decreasing tendency in NRS and the number of rescue doses was observed. We also confirmed the safety of the drug by evaluating these changes in blood concentration. These results suggested that methadone tablets may be safely administered via a simple suspension method. However, based on the experience of a single case, we could not conclude the safety of administering methadone tablets via a simple suspension method. Therefore, further investigations would be required in the future concerning these aspects.

Advances in anticancer treatment have led to more extended treatment periods and the aging of cancer survivors.[10] We have previously reported a case in which a patient undergoing outpatient chemotherapy had difficulty in continuing to take methadone due to nausea, so he switched to another injectable opioid analgesic, which was not as effective in controlling his pain.[11] Controlling pain with other opioid analgesics after discontinuing methadone may be difficult in patients with conditions requiring methadone. Accordingly, controlling intractable pain with methadone tablets is necessary in such patients, even after oral administration becomes difficult. In such cases, tube administration of methadone tablets using a simple suspension method may be more suitable. In Japan, where no dosage options other than oral forms are available, administering methadone using the simple suspension method would be a blessing for these patients.

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Author Disclosure Statement

No competing financial interests exist.

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