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Three Cases of Neuropathic Pain With Effective Pain Relief After Switching From Hydromorphone to Oxycodone

Ichiro SUTOU*, Toshihiko NAKATANI, Tatsuya HASHIMOTO, Yoji SAITO
Palliative Care Center, Shimane University Hospital, Izumo, Shimane 693-8501, Japan
**Current affiliation: Municipality Okuizumo Hospital, Okuizumo-cho, Shimane 699-1511, Japan*
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We have reported three cases in which switching from hydromorphone to oxycodone provided effective analgesia for neuropathic pain caused by cancer. Case 1 was ovarian cancer, case 2 was lung cancer and case 3 was carcinoma of unknown origin. We diagnosed parts of the pain were neuropathic pain caused by lymph node metastasis or bone metastasis of cancer in flow chart of grading system for neuropathic pain diagnosis chart. There are few reports on the effect of hydromorphone on neuropathic pain, the efficacy of oxycodone has been reported in a comparison of hydromorphone-induced morphine and oxycodone. It has been suggested that different effects for neuropathic pain between hydromorphone and oxycodone are due to the activation of GIRK1/KIR3 channels in the ventrolateral periaqueductal gray matter region. The activation mechanism induces antinociceptive effects by suppressing gamma-aminobutyric acid release. In our experience, oxycodone seemed to have a better effect on neuropathic pain than hydromorphone. Therefore, we believe that early use of oxycodone for cancer pain, in which activation-mediated neuropathic pain is considered to predominate in clinical practice, is likely to provide effective pain relief and improve patients' QOL.

Keywords: neuropathic pain, cancer pain, oxycodone, hydromorphone

Corresponding author: Toshihiko NAKATANI, M.D., Ph.D
Palliative Care Center, Shimane University Hospital, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan
Tel: +81-853-20-2237
Fax: +81-853-20-2347
E-mail: tnktn@med.shimane-u.ac.jp

INTRODUCTION

Both hydromorphone and oxycodone have excellent analgesic effects as opioids and are widely used for cancer pain in the palliative care field because they have fewer side effects than morphine hydrochloride [1, 2]. In addition, oxycodone has been suggested to be effective in treating neuropathic pain in experiments using cancer pain models [3]. Clinically, oxycodone has been reported to be effective in treating neurological side effects of chemotherapy [4]. However, as far as we could find, there was no report that clarified the efficacy of oxycodone for neuropathic pain. Furthermore, there were no similar reports on morphine or hydromorphone.

In the three cases we experienced, oxycodone, a common first-line drug for cancer pain, was used. It was not effective in relieving pain, so the patient was hospitalized and switched to hydromorphone. But hydromorphone also was not effective in relieving pain. Since all these cases were considered neuropathic pain, we switched to oxycodone again and performed tightening again, resulting in effective pain relief with a lower dose than hydromorphone.

CASES

Table 1 shows the details of the three cases. The primary tumors were right ovarian cancer in case 1, adenocarcinoma of the right lung in case 2, and carcinoma of unknown primary in case 3, with pelvic lymph node metastasis, right 10th rib metastasis, and right subclavian lymph node metastasis, respectively. Fig. 1 are CT images the metastatic lesion in each patient and suggesting that the pain was caused by nerve damage in the vicinity of the metastatic tumor. Although there were differences in sensory disturbance in each case, we diagnosed some of the pain as neuropathic pain caused by lymph node me-

Table 1. Baseline characteristics of the cases

Case	Age	gender	primary lesion	recurrence and/or metastatic lesion	pathological diagnosis	pain region	dominant nerve	CRP (mg/dL)	Alb (g/dL)	mGPS
1	87	F	endometrial cancer	lt. pelvic lymph nodes	endometrial adenocarcinoma	lt. lower limb	lt. femoral nerve lt. obturator nerve	0.93	2.4	2
2	68	M	lt. lung cancer	lt. ribs	adenocarcinoma	lt.chest	lt. intracostal neves	1.18	3.4	2
3	67	F	unknown	rt. subclavian lymph nodes rt. axillary lymph nodes	squamous cell carcinoma	rt. Upper limb	rt. brachial plexus	0.22	3.7	0

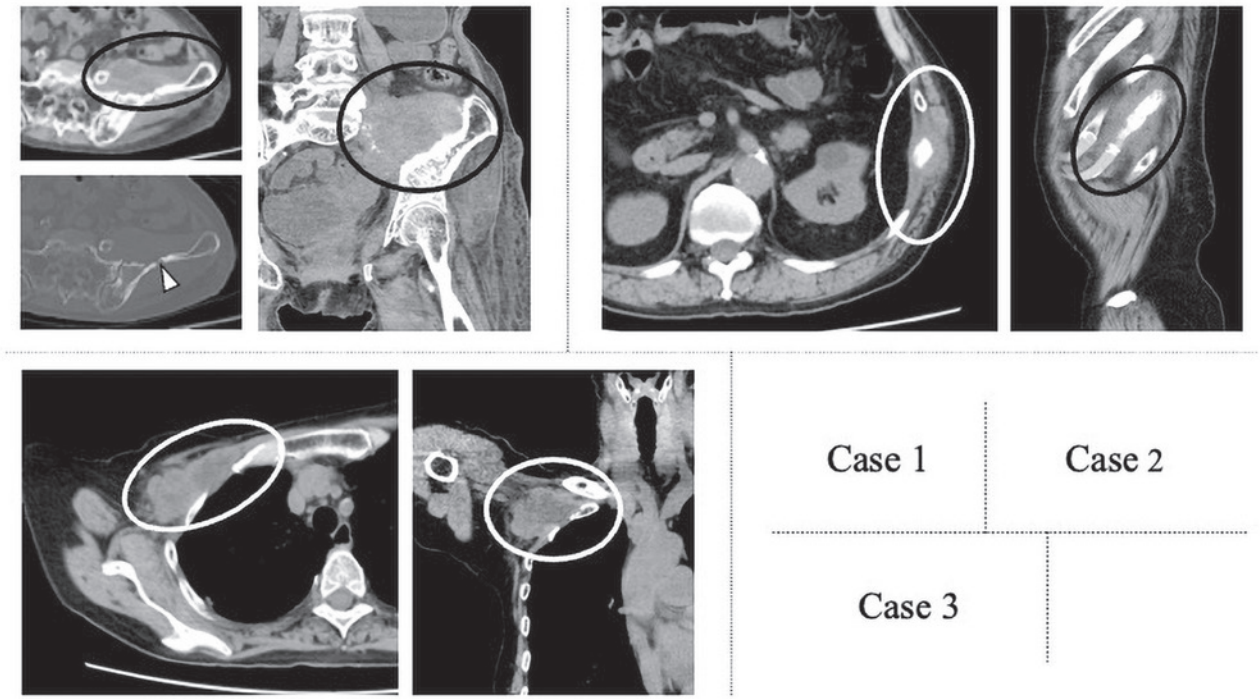

Fig. 1
CT images of each case. The lesion is indicated by a circle and a triangle.
Case 1: There is left sciatic nerve invasion and destruction of the ilium by the tumor.
Case 2: There is a mass on the left rib. Diagnosed as bone metastasis with irregular and increased bone cortex.
Case 3: There was a 60*34*35 mm metastatic lymph node tumor extending from the right axilla to the supraclavicular fossa and right brachial plexus invasion.

tastasis or bone metastasis of cancer based on the flowchart for diagnosis of neuropathic pain (Fig. 2) [5].

The blood test findings at the time of admission showed no abnormalities in complete blood count, liver function, or renal function, but the modified Glasgow Prognostic Scale [6], an index of cachexia, were 2, 2, and 0 in each case, respectively, so the presence of cachexia was suspected in cases 1 and 2.

COURSE OF TREATMENT

In cases 1 and 2, oral oxycodone and analgesic adjuvant were prescribed as prior medications in the outpatient clinic, but they were not sufficiently effective pain management with the dose increasing, so the patients were admitted for pain relief. After admission, Case 2 was switched to hydromorphone with equal analgesic doses and started on tightening. Pain was assessed by the number of rescues per day (rescues/day) and the Numeric Rating Scale (NRS), which was obtained from the patient, and the dose was increased accordingly. However, after the switch

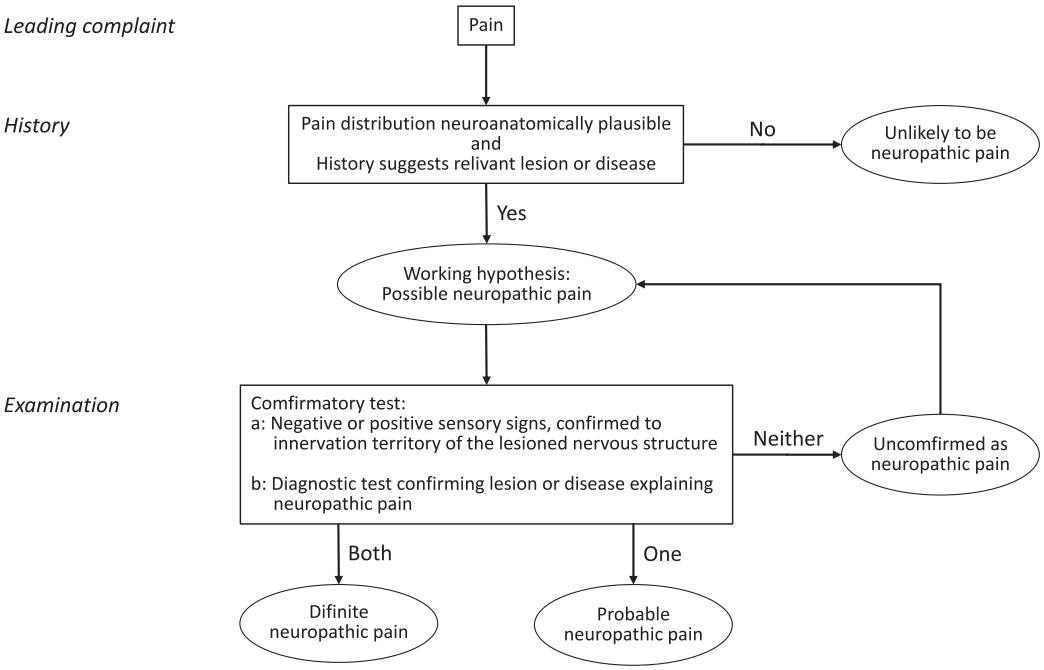

Fig. 2
Flow chart of grading system for neuropathic pain.

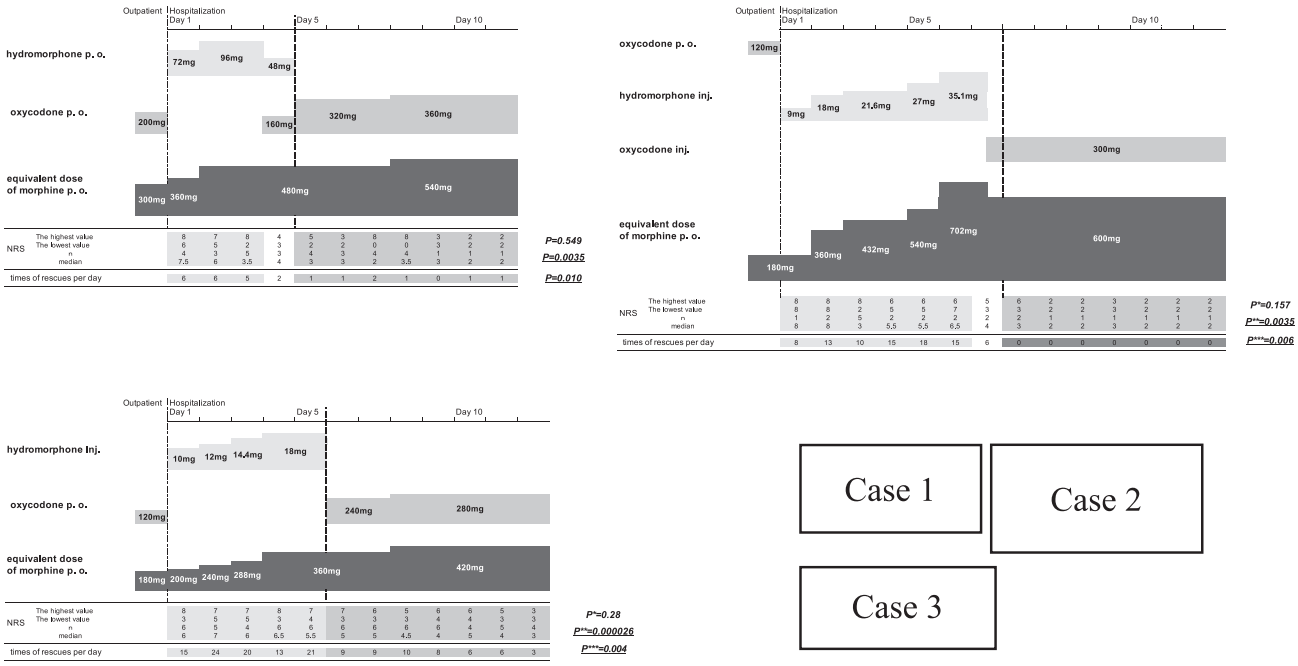

Fig. 3
Changes in opioid dose and pain assessment during the course of pain management.
P*: P-value of starting dose versus final dose of hydromorphone in NRS
P**: P-value of hydromorphone versus oxycodone, before and after switching in NRS
P***: P-value of hydromorphone versus oxycodone, before and after switching in times of rescues per day

at the time of admission, the control was still poor without improvement in pain even after increasing the dose. In addition, the patient gradually complained more of neuropathic pain-like pain, so we switched her from hydromorphone to oxycodone, the equivalent analgesic dose at that time. The course of drug administration, rescue/day, and NRS values during this treatment period are shown in Fig. 3.

The NRS and number of rescues were compared during the entire period of hydromorphone administration and one week after the switch to oxycodone. In cases 1 and 2, there was overlap between the two drugs on the day of switching, so this day was excluded from the comparison. In order to evaluate the effect of increasing the dose of hydromorphone, the dose on the day after admission and the dose immediately before the switch were also evaluated, but only the NRS was compared due to a lack of data on the number of rescues per day. Wilcoxon's signed rank test was used to determine the statistical difference of each value. The p-values are shown in Fig. 3.

There was no significant difference in the number of rescues and NRS immediately after the introduction of oxycodone and immediately before switching to oxycodone, with P*-values of 0.549, 0.157 and 0.28 for cases 1 to 3, respectively, indicating that increasing the dose of hydromorphone did not have good effect on pain relief. In the comparison before and after switching to oxycodone, the P-values (P**) for NRS were 0.0035, 0.0035, and 0.000026 and the P-values (P***) for the number of rescues were 0.01, 0.006 and 0.004. There was no exacerbation or new occurrence of adverse events due to opioids after switching.

DISCUSSION

Cancer pain is frequently observed in cancer patients, and the prevalence of pain in meta-analysis results is 39.3% after curative treatment, 55.0% during anticancer treatment, 66.4% in advanced, metastatic, or terminal stages, and 50.7% in all stages [7]. The pain of three cases is usually considered to be a mixture of nociceptive and neuropathic pain [8]. The efficacy of opioids in treating these types of cancer pains has been recognized, and opioids are widely used in Japan [9].

In our cases, we used hydromorphone and oxycodone as opioid analgesics. These drugs are synthesized from morphine (Fig. 4A) and thebaine (Fig. 4B), respectively, and are classified as semi-synthetic opioid analgesics that exert their analgesic effects by acting on the μ-opioid receptor (MOR). Both drugs have a morphinan skeleton similar to morphine, and there is little difference in their steric structures. The MORs to which both drugs bind are also G protein-coupled receptors (GPCRs) that penetrate cell membranes, and there is no significant difference in the mechanism by which opioids bind

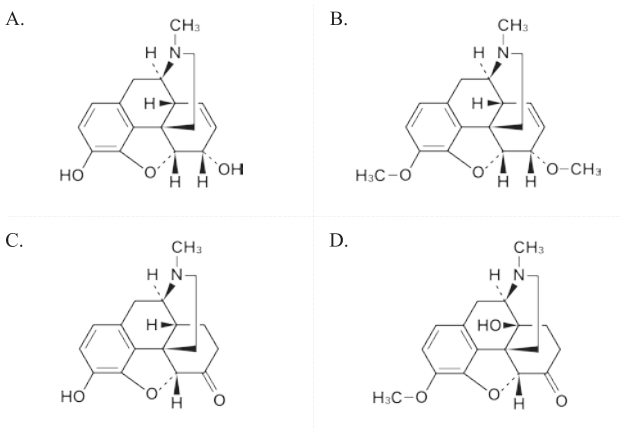

Fig. 4
Structure Formulas of Opioids.
A. Morphine ($C_{17}H_{19}NO_3$)
B. Thebaine ($C_{19}H_{21}NO_3$)
C. Hydromorphone ($C_{17}H_{19}NO_3$)
D. Oxycodone ($C_{18}H_{21}NO_4$)

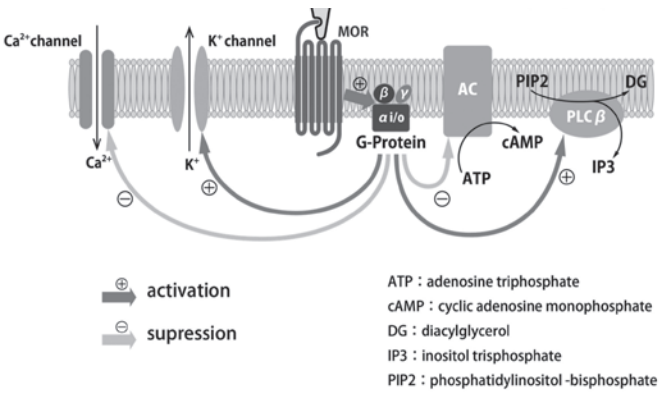

Fig. 5
Intracellular signal transduction system of MOR.
Prepared by the author based on the Clinical Guidelines for Cancer Pain Management Second Edition, page 42, Figure 1.

and produce analgesia via intracellular signaling systems as shown in Fig. 5. [1, 10, 11]. Traditionally, opioids used in clinical practice have been largely classified as MOR agonists. However, it is well known that pain management is often improved by switching from one opioid to another, commonly referred to as "opioid switching".

It has also been reported that the efficacy of opioids for neuropathic pain is low [12, 13], and that there is insufficient evidence to judge the efficacy of hydromorphone for neuropathic pain based on the results of meta-analysis [2]. On the other hand, Minami *et al*. [3] showed that oxycodone has the most pronounced effect on neuropathic pain in experiments using three kinds of mouse pain models: tail flick test, sciatic nerve ligation model, and femoral bone carcinoma (FBC) model. Clinically, oxycodone has been shown to be more effective than other opioids not only for neuropathic pain caused by cancer but also for neurological symptoms caused by anticancer drugs [4, 14]. In our three cases, the number of rescues and NRS values did not change even when the dose was increased during tightening with hydromorphone, but these values decreased significantly after switching to an equal volume of oxycodone. Although the number of cases was small, switching to oxycodone for neuropathic pain was considered effective.

Thus, it is thought that the "opioid switching" observed among opioids and the differences in pharmacological profiles for neuropathic pain may be due to differences in receptor activation [3]. In recent years, slow progress has been made to clarify these differences and to ensure appropriate use of opioids, but as of yet, no clear conclusions have been reached. However, several hypotheses have been considered, including the Biased Ligand hypothesis involving a non-G-protein intracellular signaling system via β-arrestin as the reason for MOR itself [15, 16]. In addition, it has been reported that gamma-aminobutyric acid (GABAergic) synaptic transmission, which is normally inhibitory, may be altered as a factor related to the neurotransmitter system. In other words, with the activation of P2X4 receptors in microglia, GABA released from interneurons exerts excitatory effects on second-order neurons in pain perception, and GABA-mediated inhibitory synapses are weakened, resulting in neuropathic pain [17]. Narita *et al*. [18] mentioned that the difference in their effects on neuropathic pain may be due to differences in G-protein activity in MOR between oxycodone and morphine. In the FBC model, GABAergic synaptic transmission is enhanced and acts as a descending pain regulator [19]. In the FBC model, GABAergic synaptic transmission is enhanced and transmitted to inhibit ventrolateral periaqueductal gray matter (VLPAG) neurons, which control descending pain. Unlike morphine, oxycodone has been suggested to act on MORs coupled to GIRK1/KIR3 channels in GABAergic neurons in this VLPAG region, and to induce antinociceptive effects by suppressing GABA release [20]. In addition, oxycodone actively crosses the blood-brain barrier, suggesting different pharmacokinetics in the central nervous system, including the VLPAG [19]. The biased ligand hypothesis, the opioid-dependent superior spinal cord region, and the region specificity of GIRK1/KIR3 channels have also been discussed [21]. The Biased Ligand hypothesis, opioid-dependent upper spinal cord sites, and region-specific functions of GIRK1/KIR3 channels remain to be clarified. However, it is widely suggested that oxycodone may be more effective than other opioids in the mechanism of action of neuropathic pain-dominant cancer pain.

CONCLUSION

We have reported three cases in which switching from hydromorphone to oxycodone provided effective analgesia for neuropathic pain caused by cancer. There are few reports on the effect of hydromorphone on neuropathic pain, the efficacy of oxycodone has been reported in a comparison of hydromorphone-induced morphine and oxycodone. It has been suggested that these differences are due to the activation of GIRK1/KIR3 channels in the VLPAG region, which results in an antinociceptive effect, but the mechanism has not been fully elucidated yet. In our experience, however, oxycodone seemed to have a better effect on neuropathic pain than hydromorphone. Therefore, we believe that early use of oxycodone for cancer pain, in which activation-mediated neuropathic pain is considered to predominate in

clinical practice, is likely to provide effective pain relief and improve patients' QOL.

Confict of interest

No competing financial interests exist.

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