Ten Cases of Palliation of Cancer Pain with Morphine

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Objective: With the discovery of novel opioids in recent years, it has become feasible to alleviate various forms of cancer pain. If the characteristics of individual opioids are exploited depending on pain-related factors in cancer patients may yield satisfactory pain relief with a low incidence of adverse reactions.
Methods: This study involved 10 patients (5 male and 5 female) with cancerous abdominal pain, for whom the original opioid regimen was switched to morphine alone or continued in combination with morphine. The primary disease was gastric cancer in 5 patients, and uterine cervix, ovary cancer, leukemia, malignant pleuroperitoneal mesothelioma, and colon cancer in 1 patient each. Pain assessment was carried out using the Numerical Rating Scale.
Results: In all the 10 cases, the opioid administered first was fentanyl; the pain relief was inadequate. Satisfactory pain relief was achieved in all patients by switchover to morphine alone or by concomitant administration of morphine with fentanyl.
Conclusion: Enhanced gastrointestinal motility accounts, at least in part, for cancerous abdominal pain. Further, this kind of pain can be relieved by suppression of gastrointestinal motility with morphine.

Key words: fentanyl, morphine, gastrointestinal motility, cancerous pain, opioid rotation

INTRODUCTION

In recent years, fentanyl and oxycodone preparations have become available for the treatment of cancerous pain, besides morphine. Potency is generally not considered to vary among opioids, and it is also universally acknowledged that the effects on neurogenic pain and dyspnea do not differ among opioids. Thorough knowledge about the advantages and drawbacks of the various types of opioids may enable palliative care physicians to administer the appropriate drugs to obtain the maximal effects with minimal adverse reactions. In this study, we attempted to identify the optimal drugs or combinations of drugs that would help provide relief to cancer patients.

PATIENTS AND METHODS

The study population comprised 10 patients whose medication was switched from an opioid to morphine preparations or who received morphine concomitantly with the opioid for the control of cancerous abdominal pain. These patients were selected from among those who were being cared for by a palliative care team from 2008 through 2010. The patients, 5 male and 5 female, ranged in age from 7 to 71 years (median: 59 years). The primary lesion was gastric cancer in 5 patients, and cancer of the uterine cervix, carcinoma of the ovary, acute leukemia, malignant pleuroperitoneal mesothelioma, and cancer of the colon in 1 patient each. The causes of the abdominal pain were as follows: carcinomatous peritonitis due to peritoneal dissemination in 8 patients, ischemic enteritis due to abdominal tumor in 1 patient, and graft-versus-host disease after bone marrow transplantation for leukemia in 1 patient. Pain assessment was carried out using the Numerical Rating Scale (NRS), which is a 0 to 5-point 6-grade scale. All patients, except 1 pediatric one, themselves maintained a daily record of the degree of pain in a 24-hour pain flowchart [1, 2], and the attending nurses assessed the degree of pain by using the NRS 3 times daily for all 10 patients.

The Ethics Committee of the Tokai University School of Medicine approved this study and the relevant publication policy (No. 09R-204).

RESULTS

The background characteristics and opioid medication status in 7 of the 10 patients are shown in Table 1. In all 10 cases, the baseline NRS pain score for the cancerous abdominal pain was 5, the highest score, both according to the patients' self-assessment and as assessed by the nursing staff at the beginning of intervention by the palliative care team. The opioid was fentanyl in all cases, and it was administered in the form of a transdermal system (patches) for 7 patients and by intravenous infusion for the remaining 3 patients (cases 1, 8, and 10). The fentanyl preparations were prescribed at a dosage equivalent of a 0.6–4.0 mg injection per day (median: 0.9 mg/d). As rescue medication, 20 mg fentanyl suppositories (Anpec®)

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Table 1 Cases of cancerous abdominal pain

Case	Age	Sex	Primary lesion	Cause of abdominal pain	Initial regimen Fentanyl (mg/d)	Switch/ Concomitant	Morphine after switchover (mg/d)	Pain palliation other than drug therapy	Drugs other than analgesics	NRS after switchover	Adjuvant analgesic
1	7	F	Acute myeloid leukemia	GVHD*	0.9 (IV infusion)	Switchover	60 (IV infusion)	—	—	0	—
2	59	F	Carcinoma of cervix	Cancerous peritonitis GI obstruction	0.9 (IV infusion)	Concomitant	40 (IV infusion)	Nasogastric tube	Sandostatin 300 μg	2	—
3	54	M	Gastric cancer	Cancerous peritonitis	0.6 (Transdermal)	Concomitant	60 (Enteral)	—	—	2	Gabapentin 300 mg
4	37	M	Malignant pleuroperitoneal mesothelioma	Ischemic enteritis	0.6 (Transdermal)	Switchover	30 (IV infusion)	—	—	0	—
5	71	M	Gastric cancer	Cancerous peritonitis GI obstruction	4.0 (Transdermal)	Switchover	140 (IV infusion)	Nasogastric tube	—	2	—
6	63	M	Gastric cancer	Cancerous peritonitis GI obstruction	4.0 (IV infusion)	Concomitant	200 (IV infusion)	Nasogastric tube	Sandostatin 300 μg	2	—
7	57	F	Carcinoma of ovary	Cancerous peritonitis GI obstruction	0.9 (Transdermal)	Concomitant	10 (IV infusion)	Colostomy	Sandostatin 300 μg	3	Lidocaine 500 mg
8	60	F	Gastric cancer	Cancerous peritonitis GI obstruction	1.4 (IV infusion)	Switchover	80 (IV infusion)	—	Sandostatin 300 μg	1	—
9	67	M	Gastric cancer	Cancerous peritonitis GI obstruction	3.0 (Transdermal)	Concomitant	50 (IV infusion)	—	Sandostatin 300 μg	2	—
10	68	F	Cancer of colon	Cancerous peritonitis GI obstruction	0.75 (IV infusion)	Switchover	30 (IV infusion)	—	Sandostatin 300 μg	3	—

IV, intravenous
*graft-versus-host disease

were used in case 3, and fentanyl injections were used for the remaining 9 patients. Rescue with fentanyl injections did not prove adequate for pain relief in the 9 patients. Of the 10 patients studied, 7 (cases 2, 5, and 6–10) developed symptoms of concurrent gastrointestinal obstruction. Decompression was instituted with octreotide acetate (Sandostatin®) administered by intravenous infusion in 6 patients (cases 2 and 6–10) and via a nasogastric tube in 3 patients (cases 2, 5, and 6). The rescue medication was switched from fentanyl to morphine injections in 6 patients (cases 1, 2, and 4–7), which resulted in a decrease in the NRS pain score to 2–3 in all cases. In the 10 cases studied, the total dose of morphine used was 10–200 mg/d (median: 55 mg/d). The treatment in 5 patients (cases 1, 4, 5, 8, and 10) was switched entirely to morphine, and 3 of these patients (cases 1, 4, and 5) were discharged for palliative care at home. The remaining 5 patients, whose general condition was poor (cases 2, 3, 6, 7, and 9), received concomitant treatment with fentanyl and morphine. The doses of morphine used for these patients were equivalent to or lower than those of fentanyl at the time of the switchover to morphine or morphine + fentanyl because pain relief with the opioid was inadequate. For the 3 patients (cases 1, 3, and 4) who did not have gastrointestinal obstruction, the abdominal pain disappeared after switchover to morphine, and oral ingestion became possible. Adjuvant analgesics were prescribed concurrently for 1 patient with gastric cancer and 1 patient with ovarian cancer.

DISCUSSION

Unlike morphine, fentanyl preparations may not have an adequate analgesic effect even when used at the proper doses [3, 4]. The inadequate pain relief experienced by the patients in the present series may be attributed to the diminished effect of or tolerance to fentanyl. Smith [5] described that the development of tolerance to opioids in clinical settings may be influenced by disease progression and psychological factors, making it difficult to diagnose opioid tolerance. However, we inferred that the inadequate pain relief experienced by our patients might have been a consequence of increased abdominal pain due to enhanced gastrointestinal motility rather than to the diminished effect of or development of tolerance to fentanyl. Visceralgia can be classified into (1) pain caused by capsular distension due to traction and/or swelling of the parenchymatous organs (e.g., liver and lung) and (2) pain caused by spasms or dilatation of hollow organs (e.g., gastrointestinal tract and ureter) due to ischemia or inflammation. We believe that the enhanced gastrointestinal motility may have a bearing on the latter.

Previously, it has been thought that the potency and effects do not vary among opioids. Nevertheless, individual opioids have different characteristics (Table 2). The mu (μ) type opioid receptor has been classified into the μ1 and μ2 subtypes. Moskowitz *et al.* [6] reported that the analgesic effect of opioids is mediated by the μ1 opioid receptor. This receptor mediates analgesia and miosis, whereas the μ2 opioid receptor is involved in the suppression of gastrointestinal motility and cough and in the occurrence of respiratory depression. A report by Nabeshima [7] addressed the affinity of fentanyl and morphine for the μ1 and μ2 opioid receptors. Both have a high affinity for the former, while oxycodone shows a high affinity for the latter. With regard to the selectivity of opioid receptors, the μ1 opioid receptor is remarkably responsive selectively to fentanyl, while the μ1 and μ2 receptors are modestly responsive to morphine and oxycodone (Oxycotine®). Morphine exerts antitussive, dyspnea-improving, and gastrointestinal motility-suppressing effects via the μ2 receptor. Oxycodone preparations have the advantage of being safe for patients with renal impairment, in that they can be prescribed as sustained-release products at a minimum dose of 5 mg. Among the drawbacks of oxycodone preparations is that they can only be administered via the oral route and hence cannot be administered to patients who are unable to orally ingest drugs. Another drawback is that they are associated with adverse reactions such as nausea/vomiting, constipation, and sleepiness of the same severity as those induced by morphine. Fentanyl has the advantage of being associated with a lower severity of adverse reactions than morphine. However, fentanyl preparations have no effect on cancerous cough and dyspnea, and administration via the transdermal system is disadvantageous because it is ill suited to fine-dose adjustment.

Shahbazian *et al.* [8] reported that the gastrointestinal motility-suppressing effect of opioids is mediated by the μ and κ opioid receptors. Through their animal experiments, Bardon *et al.* [9] demonstrated that morphine decreases the ingested food propulsive function of the alimentary tract and suppresses gastrointestinal motility. In the event that the pain caused by spasms or dilatation of hollow organs due to ischemia or inflammation is intensified by enhanced gastrointestinal motility, i.e., visceralgia, adequate pain relief cannot be expected from an increase in the dose of fentanyl, which rather modestly suppresses gastrointestinal motility. We interpreted the observations as possibly reflecting that suppression of gastrointestinal motility being an adverse effect of morphine relieved abdominal pain stemming from enhanced gastrointestinal motility. Furthermore, morphine relieved the abdominal pain of patients without gastrointestinal obstruction and did not cause new gastrointestinal obstructions.

Physicians specializing in palliative care must have a thorough knowledge of the characteristics of each opioid. The selection of pain-relief drugs by making the best use of the characteristics of individual opioids will help reduce the incidence/severity of adverse reactions and maximize the therapeutic effects of the drugs. The doses of morphine used in the present series of patients were equivalent to or less than those of fentanyl at the time of the switchover because of the pain relief achieved with the previous opioid, i.e., fentanyl, was inadequate. Therefore, for patients treated with an opioid, we consider it effective to switch to morphine or use morphine concomitantly with the opioid for the control of cancerous abdominal pain due to enhanced gastrointestinal motility, for example, for the control of cancerous dyspnea and cough [10–13].

Table 2 Comparison of the analgesic effects of opioids

		Fentanyl	Oxycodone	Morphine
μ opioid receptor affinity	μ1	++++	++	+++
	μ2	++	+++	++
Somatalgia		Efficacy of concomitant NSAIDs recommended	Efficacy of concomitant NSAIDs recommended	Efficacy of concomitant NSAIDs recommended
Visceralgia	Pain due to traction or capsular distension of a parenchymatous organ	Effective	Effective	Effective
	Abdominal pain wherein enhanced GI motility is involved	Not effective	Effective*	Effective
Neurogenic pain		Not effective when given alone Concomitant adjuvant analgesic recommended	Effective Concomitant adjuvant analgesic recommended	Not effective when given alone Concomitant adjuvant analgesic recommended
Dyspnea		Not effective	Not effective	Effective

GI, gastrointestinal
*Theoretically, oxycodone is considered effective since it suppresses gastrointestinal motility.

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REFERENCES

1) Faries JE, Mills DS, Goldsmith KW, Phillips KD, Orr J. Systematic pain records and their impact on pain control. A pilot study. Cancer Nurs 1991; 14: 306–13.
2) Jadlos MA, Kelman GB, Marra K, Lanoue A. A pain management documentation tool. Oncol Nurs Forum 1996; 23: 1451–2.
3) Benítez-Rosario MA, Feria M, Salinas-Martín A, Martínez-Castillo LP, Martín-Ortega JJ. Opioid switching from transdermal fentanyl to oral methadone in patients with cancer pain. Cancer 2004; 101: 2866–73.
4) Mercadante S, Ferrera P, Villari P, Casuccio A. Rapid switching between transdermal fentanyl and methadone in cancer patients. J Clin Oncol 2005; 23: 5229–34.
5) Smith HS. Opioid tolerance and dependence. In: Mao J, Chen L, eds. (Translation by Yoshizawa K, Translation Supervised by Narita T). Drugs for Pain. Tokyo: Elsevier Japan KK, 2005: 199–203 (in Japanese).
6) Moskowitz AS, Goodman RR. Autoradiographic distribution of mu1 and mu2 opioid binding in the mouse central nervous system. Brain Res 1985; 360: 117–29.
7) Nabeshima T. Dissociation of the effect of fentanyl on analgesic action and sedation. Pain Clin 2008; 29: 1407–13 (in Japanese).
8) Shahbazian A, Heinemann A, Schmidhammer H, Beubler E, Holzer-Petsche U, Holzer P. Involvement of mu- and kappa-, but not delta-, opioid receptors in the peristaltic motor depression caused by endogenous and exogenous opioids in the guinea-pig intestine. Br J Pharmacol 2002; 135: 741–50.
9) Bardon T, Ruckebusch Y. Comparative effects of opiate agonists on proximal and distal colonic motility in dogs. Eur J Pharmacol 1985; 110: 329–34.
10) Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. Ann Intern Med 1993; 119: 906–7.
11) Mazzocato C, Buclin T, Rapin CH. The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: a randomized double-blind controlled trial. Ann Oncol 1999; 10: 1511–4.
12) Watanabe N, Yasumura M, Nakagawa C, Tateyama K, Yasuda K. A case of successful treatment with a combination of morphine and a fentanyl patch in a patient suffering from cancer pain accompanied by coughing and dyspnea. Palliat Care Res 2007; 2: 310–2 (in Japanese).
13) Mercadante S. Opioid combination for cancer pain. Br J Cancer 2004; 90: 2049.