[**Original Research**]

Effect of Olanzapine on Opioid-induced Nausea and Vomiting in Cancer Patients

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(Accepted June 14, 2017)

Abstract: Opioids may be used for pain relief in cancer patients, but nausea and vomiting develop as side effects in 10–40% of these patients at the beginning of administration or as a result of a dosage increase during the treatment period. There are few high-quality studies showing that the antiemetics used clinically are effective for the inhibition of opioid-induced nausea and vomiting. This retrospective study evaluated the efficacy and safety of olanzapine administered to patients who were receiving opioids. Twenty-five patients who experienced minimal beneficial effects with metoclopramide, prochlorperazine, or other types of antiemetics, and who then received olanzapine as an additional antiemetic agent at our hospital, from 2010 through 2015, were eligible for this study. Nausea and vomiting were prevented in 0% and 12% of the patients, respectively, before the addition of olanzapine and in 56% and 80%, respectively, after the addition of olanzapine. In the statistical analysis, a significant difference ($p < 0.001$) was found between the 2 groups. The study results showed that the symptoms of nausea and vomiting improved significantly after the addition of olanzapine. This suggests that opioid-induced nausea and vomiting may be suppressed by the addition of olanzapine, which may have contributed to improved quality of life in these patients.

Key words: antiemetics, cancer patient, nausea and vomiting, olanzapine, opioid

INTRODUCTION

Cancer pain may occur in any stage. Approximately 30% of cancer patients have experienced physical pain at the time of the diagnosis; this rate increases with the progression of the cancer, and more than 70% of cancer patients suffer some type of pain in the terminal phase[1]. Selection and prescription of optimal analgesics to control the intensity and characteristics of pain may improve the quality of life (QOL) and satisfaction of many cancer patients.

In recent years, opioids are being used in cancer treatment. In Japan, various types and dosages of opioids have been used, and dosages are increasing year by year. However, the levels of these dosages are extremely low in comparison with that used in other countries, which means pain control may be less effective in patients in Japan[2].

Nausea and vomiting as adverse reactions to the administration of opioids are seen in 10–40% of patients in the early stages of treatment or with increasing dosages. When nausea and vomiting persist, pain control might be discontinued, and patients are likely to suffer from severe pain. In addition, intractable pain may develop when cancer pain remains untreated[3]. There are few high-quality studies showing that the antiemetics currently used clinically are effective for the inhibition of nausea and vomiting caused by the administration of opioids. Therefore, at present, the decision of whether a certain antiemetic may be effective for this purpose relies on clinical experience[4–6]. There is no recommendation in the latest Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guidelines in this respect[7, 8].

Therapeutic agents used as the first choice for the control of opioid-induced nausea and vomiting include dopamine receptor antagonists, gastrointestinal peristalsis agents, and antihistamines. Second-choice agents include a combination of 2 of the first-choice agents or 1 of the following 3 agents: atypical antipsychotics, phenothiazine antipsychotics, and serotonin antagonists. Olanzapine is widely used in the mental disorder field as a multi-acting receptor-targeted antipsychotic (MARTA)—an atypical antipsychotic agent. Recent descriptive studies on intractable nausea have suggested the use of atypical antipsychotics, such as olanzapine and risperidone[9]. Olanzapine is regarded as a second-line agent, because it has a D_2 receptor inhibitory effect, but there is little well-defined evidence for this. Although the useful-

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ness of olanzapine alone has already been reported, there are no studies on the efficiency and safety of adding olanzapine for preventing nausea and vomiting when existing antiemetic agents have proven ineffective. Therefore, we planned a retrospective clinical study to assess the usefulness and safety of olanzapine for preventing nausea and vomiting in patients who were receiving opioids.

MATERIALS AND METHODS

1. Study patients

We used a retrospective and observational method for this study. We reviewed medical and medication records acquired between January 2010 and December 2015 at Osaka General Medical Center, Osaka, Japan. Patients aged between 20 and 85 years with cancer pain and who received opioids for cancer pain were included. We examined the outcomes of 39 patients who were administered olanzapine in addition to prochlorperazine, metoclopramide, or another antiemetic for the relief of nausea and vomiting. Fourteen patients were excluded from the analysis: 1 was defused, 2 had diabetes mellitus, and 11 had undergone chemotherapy within 2 weeks before receiving antiemetics. A total of 25 patients (14 male and 11 female) met the inclusion criteria. Before commencing olanzapine treatment, the patients were given an explanation that this was a prospective clinical study related to off-label use.

2. Survey and evaluation method

We retrieved the following data from the medical records of the patients retrospectively: age, gender, medication, treatment history, clinical laboratory data, treatment-emergent event for nausea and vomiting, and the side effects of medication. We used the Common Terminology Criteria for Adverse Events (CTCAE ver. 4.0) as the criteria for evaluation of nausea and vomiting. These criteria are based on the degree of the intensity of the symptoms. The severest symptoms, measured according to "grade" and that could be analyzed, of nausea and vomiting within several days before and after administration of olanzapine, were recorded for comparison between groups. The efficacy of the treatment was determined according to the inhibition rate; that is, the proportion of patients displaying symptoms of nausea and vomiting defined as "Grade 0," which had not emerged and were completely inhibited[10, 11]. In addition, we divided the 25 patients into 3 groups according to the antiemetic agents that were administered before the addition of olanzapine: the prochlorperazine (PRO), metoclopramide (MET), and prochlorperazine + metoclopramide (PRO + MET) groups. We examined the inhibition rates of nausea and vomiting before and after the administration of olanzapine in each group, and we counted the number of patients for each grade of vomiting in each group. The sequential changes of the vomiting inhibition rates for 2 days before and after the administration of olanzapine were classified according to the antiemetic agents.

3. Statistical analysis

Statistical analysis was performed on the EZR (Easy R) software. We used the Wilcoxon signed-rank test, and a p-value of less than 0.05 was considered statistically significant. The primary endpoint was the nausea and vomiting control rate.

4. Ethical considerations

This study was approved by an ethics committee of Osaka General Medical Center (approval number: 27-S1501). The doctor verbally explained to patients and families that olanzapine was not covered by insurance for this indication, and consent was obtained. This research was conducted in accordance with the Helsinki Declaration, and we processed the data so that individual patients could not be identified and privacy was ensured.

RESULTS

1. Patient characteristics

In this study, 39 patients were selected. Fourteen of these were excluded from analysis because of various reasons, such as administration of chemotherapy within 2 weeks before the administration of antiemetics. Twenty-five patients could be included in the study. The patients' backgrounds are shown in Table 1. There were 14 male and 11 female patients, with an age of 63.4 ± 11.7 years (mean ± standard deviation [*SD*]) and body mass index (BMI) of 20.1 ± 4.2 (mean ± *SD*); 84% of the patients had a performance status (PS) of 3 or 4. Olanzapine was administered orally in tablet form at an average dose of 4.0 mg per day. The antiemetic drugs administered before olanzapine were as follows: PRO (5 patients), MET (12 patients), PRO + MET (6 patients), domperidone (1 patient), and no concomitant medicine (1 patient). The average dose of each drug per day was as follows: PRO (14.5 ± 1.5 mg), MET (tablet: 10.0 ± 4.1 mg, injection: 17.9 ± 7.0 mg), and domperidone suppository (120 mg). Since olanzapine was added to cases where administration of opioids, such as morphine, oxycodone, and fentanyl, and control of nausea and vomiting with standard approaches was difficult, the frequency of nausea and vomiting up to the administration of olanzapine was similar, regardless of the type of opioid used.

2. Inhibition rates of nausea and vomiting

Table 2 shows the inhibition rates and the number of patients by grade for nausea and vomiting before and after administration of olanzapine. The inhibition rate shows the percentage of patients with Grade 0 relative to the total patients. The nausea inhibition rate significantly increased from 0% to 56% before and after the addition of olanzapine ($p < 0.001$). The vomiting inhibition rate increased significantly from 12% to 80% ($p < 0.001$).

The details of the vomiting evaluation (Grade 0 to 4) before and after the addition of olanzapine to each type of antiemetic agent are shown in Table 3. The number of Grade 0 patients before the addition of olanzapine was 1 each in the PRO, MET, and PRO + MET groups, and after the addition of olanzapine was 5 in the PRO, 10 in

Table 1 Characteristics of the patients ($n = 25$)

Gender	male	14 (56%)
	female	11 (44%)
Age (years)		63.4 ± 11.7
Performance status	1	0 (0%)
	2	4 (16%)
	3	6 (24%)
	4	15 (60%)
BMI		20.1 ± 4.2
Treatment history of chemotherapy	presence	21 (84%)
	absence	4 (16%)
Number of patients by olanzapine dose	1.25 mg	1 (4%)
	2.5 mg	6 (24%)
	5.0 mg	17 (68%)
	7.5 mg	1 (4%)
Mean ± *SD* (mg)		4.0 ± 1.4
Type of opioid at the start of administration of olanzapine		Oral morphine conversion amount Median (range)
Fentanyl patch		13 (52%) 60 (30–180) mg
Fentanyl injection		3 (12%) 60 (10–70) mg
Oxycodone tablet		7 (28%) 30 (15–60) mg
Oxicodone injection		1 (4%) 450 (450) mg
Morphine capsule		1 (4%) 210 (210) mg
Morphine injection		2 (8%) 60 (20–100) mg
Oral morphine conversion amount; Median (range)		60 (10–450) mg
Number of days until administration of olanzapine after starting opioid; Median (range)		78.4 (1–682)
Number of days administration of olanzapine: Median (range)		49.8 (2–545)
Combined medicine		
MET		12
PRO + MET		6
PRO		5
Domperidone		1
none		1
Daily average dose:		
MET tablet		10.0 ± 4.1 mg
MET injection		17.9 ± 7.0 mg
PRO		14.5 ± 1.5 mg
Domperidone suppository		120 mg
Types of cancer		
Esophagus, gastric cancer		5 (20%)
Liver, gallbladder, pancreatic cancer		4 (16%)
Lung cancer		3 (12%)
Ovarian, uterus cancer		3 (12%)
Tooth and oral cancer		2 (8%)
Colorectal cancer		2 (8%)
Prostate, penile cancer		2 (8%)
Breast cancer		2 (8%)
Kidney cancer		1 (4%)
Pharyngeal, laryngeal cancer		1 (4%)

Data are shown as patient number (percentage), number (range), or mean ± *SD*.

Table 2 Inhibition rates of nausea and vomiting before and after administration of olanzapine

	Number of patients before administrating olanzapine	Number of patients after administrating olanzapine	p value
Nausea grade 0	0	14	
Grade 1	8	9	
Grade 2	9	2	
Grade 3	7	0	
Grade 4	1	0	
Inhibition rate (%)	0	56	$p < 0.001$
Vomiting grade 0	3	20	
Grade 1	15	5	
Grade 2	5	0	
Grade 3	2	0	
Grade 4	0	0	
Inhibition rate (%)	12	80	$p < 0.001$

Symptoms of nausea and vomiting before and after administration of olanzapine are classified into 5 grades from Grade 0 to 4. Inhibition rate refers to the percentage of patients with Grade 0.

Table 3 Number of patients in each grade and inhibition rate for vomiting by antiemetic agent before and after the addition of olanzapine

	PRO ($n = 5$)		MET ($n = 12$)		PRO+MET ($n = 6$)	
	before	after	before	after	before	after
Grade 0	1	5	1	10	1	4
Grade 1	3	0	8	2	3	2
Grade 2	0	0	3	0	1	0
Grade 3	1	0	0	0	1	0
Grade 4	0	0	0	0	0	0
Inhibition rate (%)	20	100	8.33	83.3	16.7	66.7
p value	$p = 0.089$		$p < 0.05$		$p < 0.05$	

The grades and inhibition rates for vomiting are shown for 3 groups (total of 23 patients) according to the main antiemetic agents: PRO (5 patients), MET (12 patients), and PRO + MET (6 patients) groups. The inhibition rate refers to the percentage of patients with Grade 0.

Table 4 Number of patients in each grade and inhibition rate for nausea by antiemetic agent before and after the addition of olanzapine

	PRO ($n = 5$)		MET ($n = 12$)		PRO+MET ($n = 6$)	
	before	after	before	after	before	after
Grade 0	0	5	0	5	0	4
Grade 1	3	0	3	5	2	2
Grade 2	1	0	4	2	2	0
Grade 3	1	0	5	0	1	0
Grade 4	0	0	0	0	1	0
Inhibition rate (%)	0	100	0	41.6	0	66.7
p value	$p = 0.0545$		$p < 0.05$		$p < 0.05$	

The grades and inhibition rates for nausea are shown for 3 groups (total of 23 patients) according to the main antiemetic agents: PRO (5 patients), MET (12 patients), and PRO + MET (6 patients) groups. The inhibition rate refers to the percentage of patients with Grade 0.

the MET, and 4 in the PRO + MET group. The respective vomiting inhibition rates were 100% ($p = 0.089$), 83.3% ($p < 0.05$), and 66.7% ($p < 0.05$). Vomiting of Grade 2 or higher was not observed after administration of olanzapine, irrespective of the type of concomitant medication.

The details of the nausea evaluation (Grade 0 to 4) before and after the addition of olanzapine to each type of antiemetic agent are shown in Table 4. There were no Grade 0 patients before the addition of olanzapine. After the addition of olanzapine, the number of Grade 0 patients was 5 in the PRO, 5 in the MET, and 4 in the PRO + MET groups. The respective nausea inhibition rates were 100% ($p = 0.0545$), 41.6% ($p < 0.05$), and 66.7% ($p < 0.05$).

The sequential changes in the vomiting inhibition rate for 2 days before and after the addition of olanzapine for each antiemetic are shown in Fig. 1.

3. Side effects

Regarding side effects caused by olanzapine in the 25 patients, somnolence was exhibited in 1 patient and

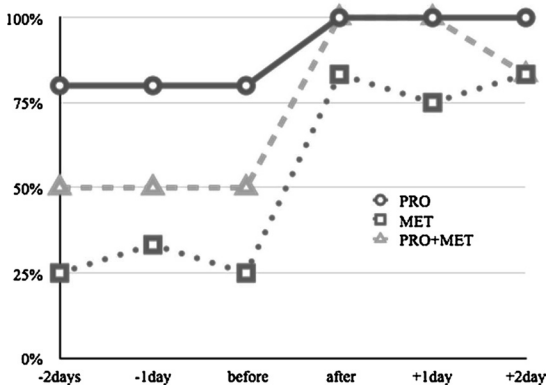

Fig. 1 Changes in vomiting inhibition rate for 2 days before and after addition of olanzapine. The inhibition rates for vomiting are shown for 3 groups (total of 23 patients) according to the main antiemetic agents: PRO (5 patients), MET (12 patients), PRO + MET (6 patients).

raised blood glucose concentration was observed in 3 patients. Although the patient with somnolence requested discontinuation of the drug, the sleepiness was minor, at Grade 1 or less. Regarding the increase in blood glucose levels, the blood glucose levels remained within the normal range in the 3 patients with an increased fasting blood glucose level within 10 mg/dl; severe hyperglycemic symptoms were not observed. No other adverse events were observed.

DISCUSSION

Nausea and vomiting are side effects of opioid use for analgesia in cancer patients, but may be associated with various factors, such as therapeutic agents (e.g., digitalis, antimicrobial agents, iron preparations, and anticancer drugs), gastrointestinal diseases (e.g., gastric ulcer, constipation, diarrhea, and intestinal obstruction), electrolyte abnormalities (e.g., high calcium and hyponatremia), infectious diseases, hyperglycemia, lesions of the central nervous system (e.g., brain metastasis and cancerous meningitis), and radiation therapy. Therefore, the cause of nausea and vomiting needs to be assessed in each case and treated appropriately. In Japan, olanzapine was launched in 2001 for the treatment of schizophrenia and bipolar disorder. The mechanism of action for olanzapine involves the inhibition of multiple chemoreceptors, such as histamine, dopamine, adrenaline, and muscarinic receptors[12, 13]. In addition, olanzapine is believed to have an antiemetic effect. Currently in Japan, olanzapine is not regularly used as a first-line antiemetic agent, and use as an antiemetic is considered off-label. In this study, we compared the results before and after the combination of olanzapine with existing antiemetic agents. The reason for the additional administration of olanzapine was that insufficient antiemetic effect was obtained by administration of another antiemetic agent, while opioid was continuously administered to maintain pain relief. Although this study included a small number of cases and had a retrospective design, the results showed that the percentages of patients in which nausea and vomiting were inhibited were significantly greater after, rather than before, the addition of olanzapine. The number of days until administration of olanzapine after starting opioids was 78.4 (1–682) days, which showed a considerable variation. The variation was related to the fact that the symptoms of nausea and vomiting became stronger as the dose of opioid increased, due to increased pain, or at the beginning of opioid treatment.

As for the inhibition rates after the addition of olanzapine for each antiemetic agent, the inhibition rate was 100% with a p-value > 0.05 for both nausea and vomiting in the PRO group. It is considered that no statistically significant difference was obtained because the sample size was small. The inhibition rate of vomiting in the PRO + MET group was 66.7%; although the inhibition rate was lower than that in the other 2 groups, even if it was inevitable to use both drugs in combination, it appears that a clear effect was obtained by addition of olanzapine. In future, we aim to recruit more cases to verify the safety and effectiveness of this treatment.

The main side effects of olanzapine are somnolence, weight gain, akathisia, and appetite promotion, but it is considered that the extrapyramidal symptoms and akathisia are both considered mild and the side effects are less severe than those encountered with typical antipsychotics[9, 14]. In our study, extrapyramidal symptoms were not observed, but concomitant use of an antiemetic agent is likely to induce extrapyramidal disorder. If it is unavoidable to administer olanzapine additionally, we consider that side effects should be monitored, and the drug should be discontinued as soon as nausea and vomiting are controlled.

In addition, the appetite stimulation, which is a side effect of olanzapine, can be expected to have a positive effect for cancer patients whose oral intake is decreased. It is thought that this may contribute to an improvement in the QOL of these patients.

Olanzapine is metabolized in the liver, and the metabolizing enzyme CYP1A2 is mainly involved[12]; therefore, drug interactions are minimal and olanzapine is a potentially useful agent in combination with multiple agents for patients with cancer pain. It has also been reported that the 5-HT_2 blocking action of olanzapine leads to improved sleep[15], and has anxiolytic effect[16], and a sleep regulating action, which may alleviate anxiety and insomnia, and help relieve mental stress in cancer patients.

Use of olanzapine as an antiemetic agent increases the available options for control of nausea and vomiting, and may contribute to improved QOL in cancer patients, because effective suppression of opioid-induced nausea and vomiting may lead to improved compliance with opioid use and improved pain control. We were unable to determine the percentage of patients who required treatment for their severe opioid-induced nausea and vomiting with olanzapine because of the great differences between individuals and complications. In future, we plan to

investigate the differences in antiemetic effects by using a combination of olanzapine and MET or PRO at the time when opioid is introduced. In addition, we plan to compare the antiemetic effects among different dosages and treatment durations of olanzapine.

Conflicts of Interest

The authors declare that they have no competing interests.

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

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