Predictors for Effectiveness of Naldemedine in Patients with Cancer Pain: A Retrospective, Single-Institution Analysis

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Abstract

Purpose

To identify predictors for the effectiveness of naldemedine.

Methods

Participants comprised 106 advanced cancer patients receiving pain treatment with opioids who were prescribed naldemedine for OIC at Seirei Hamamatsu General Hospital in Japan between November 2016 and June 2021. For the regression analysis of factors associated with OIC, variables were extracted manually from medical charts. The effectiveness of naldemedine was evaluated 3 days after administration, based on whether patients showed OIC. Presence of OIC was defined based on Rome IV diagnostic criteria. Multivariate logistic regression analysis was performed to identify predictors for naldemedine effectiveness. Values of $P < 0.05$ (two-tailed) were considered significant.

Results

Significant factors identified included chemotherapy with taxanes within 1 month of evaluation of naldemedine effectiveness (odds ratio [OR] = 0.063, 95% confidence interval [CI] = 0.007–0.568; $P = 0.014$), and addition of or switching to naldemedine due to insufficient prior laxatives (OR = 0.352, 95%CI = 0.129–0.966; $P = 0.043$).

Conclusion

No chemotherapy that included taxanes within 1 month of evaluation of naldemedine effectiveness and no addition of or switching to naldemedine due to insufficient prior laxatives were identified as predictors for effectiveness of naldemedine in patients with cancer pain.

Introduction

Opioid-induced constipation (OIC) is one of the most common adverse events of opioid therapy and can severely reduce quality of life (QOL) [1–3]. OIC is common among patients with advanced cancers, with a prevalence of approximately 51–87% among patients receiving opioids for pain management [1–5]. Naldemedine is the newest orally available, peripheral-acting μ -opioid receptor antagonist (PAMORA). Naldemedine improves OIC by binding to opioid receptors in the gastrointestinal tract and antagonizing opioid analgesics. The analgesic effects of many opioid analgesics are expressed mainly via the central μ -opioid receptors. Naldemedine is a PAMORA designed so as not to inhibit the action of opioid analgesics in the central nervous system [6, 7]. Naldemedine has also been shown to improve patient-rated constipation-related symptoms and QOL [6–10]. Previous studies have suggested that no baseline

variables affect the efficacy or safety of once-daily oral naldemedine 0.2 mg in patients with OIC [11, 12]. On the other hand, in daily clinical practice, some advanced cancer patients have shown insufficient OIC control even while receiving naldemedine [3, 12]. This retrospective study was thus undertaken to identify predictors for the effectiveness of naldemedine, to help guide future strategies toward improving QOL in advanced cancer patients receiving pain treatment with opioids.

Patients And Methods

Study Period and Participants

This study retrospectively analysed 139 patients with cancer pain prescribed naldemedine for OIC at Seirei Hamamatsu General Hospital in Japan between November 2016 and June 2021. All study protocols were approved by the Medical Ethics Review Committee at Seirei Hamamatsu General Hospital (approval no. 3310) and the Faculty of Pharmacy at Osaka Medical Pharmaceutical University (approval no. 0088).

Extraction of Variables

Variables associated with the effectiveness of naldemedine were extracted from clinical records and used for regression analysis. Variables extracted were factors potentially affecting the effectiveness of naldemedine: demographic data (age, height, weight, body surface area, body mass index [BMI]), Eastern Cooperative Oncology Group performance status, daily dosage of opioid in milligrams of morphine-equivalents, types of concomitant laxatives, types of opioids, stage of cancer, anti-cancer drugs administered within 1 month of the evaluation of naldemedine effectiveness, timing of naldemedine administration, and cancer type.

The effectiveness of naldemedine was evaluated 3 days after administration, based on whether the patient had OIC. The presence of OIC was defined based on Rome IV diagnostic criteria [3]. Details of the Rome IV diagnostic criteria for the diagnosis of OIC used in this study have been published previously [13–15].

Statistical Analysis

The analytical procedure employed was logistic regression, with the response = Y being a binary categorical variable (naldemedine effective or naldemedine not effective) and evaluated simultaneously with multiple predictors of effectiveness of naldemedine = X . To improve accuracy, predictors that were not essential to explain the response = Y were excluded.

Independent variables were analysed for multicollinearity (correlation coefficient $|r| \geq 0.7$), since correlations among variables can lead to unreliable and unstable results of regression analyses. Independent variables were extracted based on the strength of the correlation with effectiveness of naldemedine or clinical significance. First, univariate logistic regression analyses between outcomes and each potential independent variable were performed. Subsequently, a multivariate logistic regression

model was constructed by employing the forward-backward stepwise selection procedure with the resulting candidate variables.

For all statistical analyses, values of $P < 0.05$ (two-tailed) were considered significant. All analyses were conducted using JMP version 14.3.0 (SAS Institute, Cary, NC).

Results

All 139 patients were newly prescribed naldemedine, but 33 patients were excluded from this study due to insufficient data. Table 1 presents the clinical characteristics of the remaining 106 enrolled patients, potential variables related to OIC, and the results of univariate analyses. The forward-backward stepwise selection procedure identified the following candidate variables: BMI, chemotherapy with taxane within 1 month of evaluation of naldemedine effectiveness, daily dosage of opioid, use of naldemedine prescription within 2 days of opioid initiation, and addition of or switching to naldemedine due to insufficient prior laxatives.

Table 1
Patient characteristics, extracted variables, and results of univariate analyses (n = 106)

	Laxative not effective (n = 42)	Laxative effective (n = 64)	P value	Odds ratio (95%CI)
Demographic data				
<i>Sex, male, n (%)</i>	30 (71.4)	39 (60.9)	0.269	0.62 (0.27– 1.44)
<i>Age (y), median (range)</i>	42–88 (69)	42–89 (70)	0.777	1.01 (0.97– 1.04)
<i>Height (cm), median (range)</i>	145–176 (163)	143–180 (160)	0.585	0.99 (0.94– 1.04)
<i>Weight (kg), median (range)</i>	32.5–73.7 (54)	35–84 (51.1)	0.363	0.98 (0.94– 1.02)
<i>Body mass index (kg/m²), median (range)</i>	13.0–28.9 (19.7)	14.2–28.8 (19.6)	0.434	0.95 (0.84– 1.08)
<i>Body surface area (m²), median (range)</i>	1.22–1.84 (1.58)	1.24–2.04 (1.55)	0.365	0.30 (0.02– 4.06)
<i>Eastern Cooperative Oncology Group performance status (0/1/2/3/4)</i>	0/4/21/15/2	0/8/25/24/7	0.483	1.19 (0.73– 1.94)
<i>Stage of cancer (1/2/3/4)</i>	0/3/0/39	0/2/5/57	0.062	1.01 (0.37– 3.33)
Chemotherapy given within 1 month of evaluation of naldemedine effectiveness , n (%)	19 (45.2)	23 (35.9)	0.339	0.68 (0.31– 1.50)

CI, confidence interval

*P<0.05

	Laxative not effective (n = 42)	Laxative effective (n = 64)	<i>P</i> value	Odds ratio (95%CI)
Anti-cancer drug administered within 1 month of evaluation of naldemedine effectiveness				
<i>Taxanes, n (%)</i>	7 (16.7)	2 (3.1)	0.028	0.16 (0.03–0.82)
<i>Fluorouracil, n (%)</i>	5 (11.9)	10 (15.6)	0.592	1.37 (0.43–4.34)
<i>Platinum, n (%)</i>	9 (21.4)	15 (23.4)	0.809	1.12 (0.44–2.86)
Types of opioids				
<i>Morphine, n (%)</i>	4 (9.5)	11 (17.2)	0.606	1.00 (1.00–1.01)
<i>Fentanyl, n (%)</i>	2 (4.8)	3 (4.7)	0.986	0.98 (0.16–6.15)
<i>Oxycodone, n (%)</i>	31 (73.8)	42 (65.6)	0.375	0.68 (0.29–1.60)
Daily dose, morphine-equivalents (mg), median (range)	10–144	15–576	0.606	1.00 (1.00–1.01)
Concomitant laxative				
<i>Magnesium oxide, n (%)</i>	5 (11.9)	13 (20.3)	0.265	1.89 (0.61–5.75)

CI, confidence interval

*P<0.05

	Laxative not effective (n = 42)	Laxative effective (n = 64)	<i>P</i> value	Odds ratio (95%CI)
<i>Sennoside, n (%)</i>	2 (4.8)	6 (9.4)	0.388	2.07 (0.39– 10.8)
<i>Lubiprostone, n (%)</i>	1 (2.4)	2 (3.1)	0.822	1.32 (0.12– 15.1)
Naldemedine prescription within 2 days of opioid initiation, n (%)	4 (9.5)	6 (9.4)	0.980	0.98 (0.26– 3.71)
Addition of or switching to naldemedine due to insufficient prior laxative, n (%)	29 (69.0)	34 (53.1)	0.105	0.51 (0.22– 1.15)
Cancer type				
<i>Colon, n (%)</i>	3 (7.1)	7 (10.9)	0.516	1.60 (0.39– 6.56)
<i>Gastric, n (%)</i>	1 (2.4)	4 (6.3)	0.376	2.73 (0.29– 25.3)
<i>Pancreatic, n (%)</i>	13 (31.0)	15 (23.4)	0.392	0.68 (0.29– 1.64)
<i>Esophageal, n (%)</i>	3 (7.1)	4 (6.3)	0.856	0.86 (0.18– 4.08)
<i>Lung, n (%)</i>	6 (14.3)	10 (15.6)	0.851	1.11 (0.37– 3.33)

CI, confidence interval

*P<0.05

	Laxative not effective (n = 42)	Laxative effective (n = 64)	<i>P</i> value	Odds ratio (95%CI)
<i>Breast, n (%)</i>	0	3 (4.7)	-	-
<i>Head and neck, n (%)</i>	9	10 (15.6)	0.47	0.69 (0.25–1.88)
<i>Urologic, n (%)</i>	4 (9.5)	4 (6.3)	0.54	0.63 (0.15–2.68)
CI, confidence interval				
* <i>P</i> <0.05				

Multivariate logistic regression analysis was performed using these variables. Significant factors identified included chemotherapy with taxanes within 1 month of evaluation of naldemedine effectiveness (odds ratio [OR] = 0.063, 95% confidence interval [CI] = 0.007–0.568; *P* = 0.014), and addition of or switching to naldemedine due to insufficient prior laxatives (OR = 0.352, 95% CI = 0.129–0.966; *P* = 0.043) (Table 2).

Table 2

Results of multivariate ordered logistic regression analysis for variables extracted by forward-backward stepwise selection procedure (n = 106)

Variable	<i>P</i> value	Odds ratio	95% confidence interval	
			Lower endpoint	Upper endpoint
Body mass index	0.098	0.890	0.776	1.022
Taxanes	0.014*	0.063	0.007	0.568
Daily dosage in morphine-equivalents (mg)	0.585	1.002	0.995	1.009
Naldemedine prescription within 2 days of opioid initiation	0.268	0.411	0.085	1.981
Addition of or switching to naldemedine due to insufficient prior laxative	0.043*	0.352	0.129	0.966
* <i>P</i> <0.05				

Discussion

The multivariate logistic regression analysis performed in this study showed that predictors for naldemedine effectiveness included chemotherapy with taxanes within 1 month of evaluation of naldemedine effectiveness and addition of or switching to naldemedine due to insufficient prior laxatives.

The results of this study showed that OIC was poorly controlled when chemotherapy with taxane was given within 1 month of evaluation of naldemedine effectiveness. Taxanes are anticancer drugs that have a side effect of constipation due to neuropathy [16]. Taxane-induced neuropathy persists for a long period in clinical practice. If taxanes was administered within 1 month of evaluation of naldemedine effectiveness, side effects may persist. OIC control may thus be difficult. On the other hand, naldemedine is primarily metabolized by cytochrome P450 3A4 (CYP3A4) to form nor-naldemedine [17]. In this study, some patients were receiving chemotherapy with taxanes at the time of evaluation of naldemedine effectiveness. Molecular species such as CYP3A4 are involved in metabolism of taxanes such as paclitaxel and docetaxel [18, 19]. Although there are no reports of drug-drug interactions between naldemedine and taxanes, it is necessary to consider the possibility to reduce naldemedine effectiveness due to drug-drug interactions, especially in patients undergoing chemotherapy with taxanes. This point needs further verification in daily clinical practice. In recent years, new opioid prescriptions are often made by oncologists during chemotherapy, rather than by palliative care physicians. Oncologists who prescribe opioids need to consider OIC control during chemotherapy, particularly in patients receiving taxane-based chemotherapy.

Addition of or switching due to insufficient prior laxatives was also extracted as a risk factor for OIC. Naldemedine is a PAMORA, and the mechanism of action clearly suggests that the shorter the period of exposure to opioids, the more likely the effects of naldemedine are to manifest. On the other hand, in the present study, the factor “naldemedine prescription within 2 days of opioid initiation” was not extracted as a significant factor. Some of the patients were undergoing chemotherapy at the time of evaluation of naldemedine effectiveness. In other words, the serotonin receptor antagonist may have also acted on serotonin receptors in the intestine and decreased intestinal motility [20]. The guidelines for OIC also suggest that classic laxatives should be used first, with the use of novel constipation treatments or PAMORA recommended only if the effects prove insufficient [21–23]. The appropriate timing of naldemedine administration needs to be verified in the future.

Several limitations to the current study need to be considered. First, the retrospective nature of the study may have decreased the validity of the data obtained. Second, since this study was performed at a single institute, prospective studies involving multiple centres are needed to confirm the results.

In conclusion, no administration of a chemotherapeutic regimen that included taxanes within one month before the evaluation of naldemedine effectiveness and no addition of or switching to naldemedine due to insufficient prior laxatives were identified as predictors of effectiveness of naldemedine in advanced cancer patients with cancer pain. However, our findings need to be confirmed in further studies. Nevertheless, these results may assist to improve QOL among advanced cancer patients with cancer pain.

Declarations

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Author contributions YK: concept and design, data analysis, data interpretation, manuscript writing; MS, YI, SS & KY: concept and design, data acquisition, data interpretation; MU: concept and design, data interpretation, supervision of the manuscript. All authors read and approved the final manuscript.

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Data availability Data not available due to ethical restrictions.

Code availability Not applicable

Ethical approval

The Medical Ethics Review Committee of Seirei Hamamatsu General Hospital approval no.3310 and Faculty of Pharmacy, Osaka Medical Pharmaceutical University approved this study, approval no.0088. All procedures were performed in accordance with the ethical standards of the Seirei Hamamatsu General Hospital and Osaka Medical Pharmaceutical University of Medicine Institutional Medical Ethics Review Committee and the 1964 Declaration of Helsinki and its later amendments. No prospective studies with human participants or animals were performed by any of the authors for this article.

This study retrospectively analysed 139 patients with cancer pain prescribed naldemedine for OIC at Seirei Hamamatsu General Hospital in Japan between November 2016 and June 2021. All study protocols were approved by the Medical Ethics Review Committee at Seirei Hamamatsu General Hospital (approval no. 3310) and the Faculty of Pharmacy at Osaka Medical Pharmaceutical University (approval no. 0088).

Consent to participate

Given the retrospective nature of this work, the need to obtain informed consent was waived for the individual participants included in the study, in accordance with the standards of the Seirei Hamamatsu General Hospital and Osaka Medical Pharmaceutical University of Medicine Institutional Medical Ethics Review Committee.

Consent for publication

All authors give their consent for this manuscript to be published in *Supportive Care in Cancer*.

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