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Factors affecting the effect of naldemedine for opioid-induced constipation: a single-institution, retrospective analysis

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Naldemedine is the newest orally available, peripherally selective μ-opioid receptor antagonist blocker approved for opioid-induced constipation (OIC) treatment in adult patients. On the other hand, some patients have insufficient OIC control even with naldemedine. Thus, this retrospective study was conducted to identify factors affecting the effect of naldemedine. The participants were 210 patients who had received naldemedine at our institute between June 2017 and August 2019. Variables associated with alleviation of OIC were extracted from clinical records and used for regression analysis. The effect of naldemedine was determined according to the degree of constipation. The degree of constipation was categorized as grade 0 – 2 with reference to the CTCAE version 5.0. Multivariate ordered logistic regression analysis was conducted to identify factors affecting the effect of naldemedine. Use of naldemedine within 2 days of opioid initiation [odds ratio (OR) =0.346, 95% confidence interval (CI) =0.173-0.693; *P* = 0.003], concomitant use of anticholinergics (OR = 2.033, 95% CI = 1.150-3.594; *P* = 0.015), tramadol (OR = 0.488, 95% CI = 0.250-0.953; *P* =0.036), and chronic non-cancer pain (OR = 0.429, 95% CI = 0.197-0.937; *P* = 0.034) were identified as significant factors related to the effect of naldemedine.

1. Introduction

Opioid-induced constipation (OIC) is one of the most common adverse events (AEs) of chronic opioid therapy and can severely reduce patients' quality of life (QOL) (Bell et al. 2009; Farmer et al. 2018; Müller-Lissner et al. 2017). μ-Opioid receptors, expressed mostly on myenteric and submucosal neurons throughout the gastrointestinal (GI) tract, are mostly responsible for the inhibition of propulsive motility by opioids and other AEs.

Naldemedine is the newest orally available, peripherally selective μ-opioid receptor antagonist blocker approved for OIC treatment in adult patients. Naldemedine improves OIC by binding to opioid receptors in the GI tract and antagonizing opioid analgesics. The analgesic effects of many opioid analgesics are expressed mainly *via* the central μ-opioid receptor. Naldemedine is a peripheral μ-opioid receptor antagonist (PAMORA) designed so as not to inhibit the action of opioid analgesics in the central nervous system (Katakami et al. 2017; Webster et al. 2018). In phase III trials, naldemedine was more effective than placebo for increasing defecation frequency in patients with OIC and cancer pain or chronic non-cancer pain (Katakami et al. 2017; Webster et al. 2018). Naldemedine was also shown to improve patient-rated constipation-related symptoms and QOL (Katakami et al. 2017; Hale et al. 2017; Hanson et al. 2019; Webster et al. 2017, 2018). Previous studies suggested that there were no apparent baseline properties affecting the efficacy or safety of naldemedine 0.2 mg in patients with OIC (Kubota et al. 2018; Osaka et al. 2019). On the other hand, in daily clinical practice, some patients have insufficient OIC control even under naldemedine. However, factors affecting the effect of naldemedine have not been sufficiently investigated (Kubota et al. 2018).

Thus, this retrospective study was conducted to identify factors affecting the effect of naldemedine in alleviating OIC.

2. Investigations and results

2.1. Patients demographics

Of the 230 patients who had received naldemedine for alleviation of OIC, 20 were excluded from this study due to discontinuation of naldemedine (n=15) or insufficient data (n=5). Reasons for discontinuation were AEs [diarrhea (n = 3, 1.3%), nausea (n = 8, 3.5%), and headache (n=1, 0.4%)], initiation of chemotherapy with irinotecan (n=1, 0.4%), and being unable to take oral medications (n = 2, 0.9%). Table 1 shows the clinical characteristics of the 210 evaluable patients, potential variables related to the effect of naldemedine, and the results of univariate analyses. As for concomitant medication, there were no medications which are CYP3A (cytochrome P450 family 3 subfamily A) inhibitors (e.g. ketoconazole, ritonavir) that could lead to an increase in naldemedine concentration, or CYP3A inducers (e.g. carbamezapine, phenytoin) that could lead to a decrease in naldemedine concentration.

2.2 Statistical analysis

The forward stepwise selection procedure identified five variables (use of naldemedine within 2 days of opioid initiation, concomitant use of anticholinergics, tapentadol, tramadol, and chronic non-cancer pain). Multivariate ordered logistic regression analysis was performed using these variables. Use of naldemedine within 2 days of opioid initiation [odds ratio (OR) =0.346, 95% confidence interval (CI) =0.173-0.693; *P* = 0.003], concomitant use of

Table 1: Patients' characteristics, extracted variables, and results of univariate analyses (n = 210)

	Grade 0 (n = 97)	Grade 1 (n = 79)	Grade 2 (n = 34)	*P* value	Odds ratio (95% CI)
Age (y), median (range)	68 (24-90)	67 (30-84)	70 (39-91)	0.731	0.997 (0.977-1.016)
Male, n (%)	54 (55.7)	42 (53.2)	16 (47.1)	0.426	0.813 (0.487-1.355)
Daily dosage of opioid converted to morphine (mg), median (range)	20 (5-180)	30 (5-720)	30 (10-60)	0.341	1.002 (0.998-1.005)
Use of naldemedine within 2 days of opioid initiation, n (%)	34 (35.1)	17 (21.5)	3 (8.8)	0.002*	0.373 (0.120-0.696)
Opioid therapy period before naldemedine administration (days), median (range)	7 (0-2708)	24 (0-1948)	32 (0-2520)	0.638	1.000 (1.000-1.001)
Brain tumor	2 (2.1)	2 (2.5)	5 (14.7)	0.007*	5.864 (1.611-21.341)
Use of routine laxatives before naldemedine administration	40 (41.7)	66 (84.6)	22 (66.7)	<.0001*	4.071 (2.278-7.278)
Concomitant medication					
Anticholinergics, n (%)	41 (42.3)	45 (57.0)	18 (52.9)	0.090	1.560 (0.933-2.606)
Calcium channel blockers, n (%)	18 (18.6)	19 (24.1)	9 (26.5)	0.266	1.416 (0.767-2.613)
On chemotherapy, n (%)	25 (25.8)	37 (46.8)	11 (32.4)	0.069	1.645 (0.962-2.811)
Vinca alkaloids	1 (1.0)	1 (1.3)	0	0.7834	0.684 (0.045-10.31)
Taxane	2 (2.1)	16 (20.5)	1 (3.0)	0.0921	2.131 (0.883-5.139)
Platinum formulation	3 (3.1)	10 (12.8)	1 (3.1)	0.3182	1.672 (0.609-4.588)
Laxative (duplicated data)					
Magnesium oxide, n (%)	18 (18.6)	40 (50.6)	14 (41.2)	0.0002*	2.822 (1.630-4.889)
Sennosides, n (%)	8 (8.2)	19 (24.1)	16 (47.1)	<0.0001*	4.945 (2.548-9.597)
Lubiprostone, n (%)	0	2 (2.5)	3 (8.8)	0.0138*	9.838 (1.594-60.740)
Sodium picosulfate, n (%)	0	4 (5.1)	5 (14.7)	0.0014*	9.060 (2.351-34.919)
Opioids					
Morphine, n (%)	4 (4.1)	6 (7.6)	1 (2.9)	0.797	1.161 (0.372-3.618)
Oxycodone, n (%)	20 (20.6)	33 (41.8)	13 (38.2)	0.006*	2.160 (1.243-3.756)
Hydromorphone, n (%)	7 (7.2)	11 (13.9)	6 (17.6)	0.068	2.097 (0.948-4.637)
Fentanyl, n (%)	4 (4.1)	4 (5.1)	3 (8.8)	0.344	1.724 (0.558-5.323)
Tapentadol, n (%)	3 (3.1)	3 (3.8)	0 (0.0)	0.621	0.671 (0.138-3.262)
Tramadol, n (%)	59 (60.8)	22 (27.8)	10 (29.4)	<.0001*	0.292 (0.169-0.505)
Physical/physiological parameters					
Height (cm), median (range)	162.6 (140-189.5)	161 (143.6-181.2)	159.5 (143-172.6)	0.027*	0.967 (0.938-0.996)
Weight (kg), median (range)	57.75 (33.4-107.6)	51.55 (30-86.3)	51 (36-77.5)	0.003*	0.967 (0.945-0.989)
BMI (kg/m^2), median (range)	21.2 (13.2-34.8)	19.8 (11.6-29.3)	21.0 (14.4-31.1)	0.027*	0.927 (0.866-0.992)
Laboratory test					
Serum creatinine, mg/dL, median (range)	0.76 (0.24-5.38)	0.72 (0.4-3.45)	0.68 (0.39-1.43)	0.149	0.611 (0.313-1.193)
ALT, U/L, median (range)	15 (4-91)	18 (2-286)	14 (5-146)	0.235	1.006- (0.996-1.016)
Albumin, g/dL, median (range)	3.8 (2-5.1)	3.5 (2-5)	3.6 (2-4.8)	0.025*	0.637 (0.429-0.945)
Cancer pain / chronic non-cancer pain (0/1)	57/40	72/7	26/8	<0.0001*	0.271 (0.141-0.518)
Type of cancer					
Colon, n (%)	7 (7.2)	2 (2.5)	0	0.064	0.218 (0.044-1.094)
Pancreas, n (%)	4 (4.1)	10 (12.7)	3 (8.8)	0.146	1.982 (0.787-4.988)
Gastric, n (%)	6 (6.2)	4 (5.1)	0	0.259	0.476 (0.131-1.730)
Esophageal, n (%)	4 (4.1)	4 (5.1)	2 (5.9)	0.658	1.307 (0.340-4.272)
Breast, n (%)	4 (4.1)	7 (8.9)	2 (5.9)	0.418	1.539 (0.542-4.372)
Lung, n (%)	12 (12.3)	17 (21.5)	7 (20.6)	0.132	1.676 (0.857-3.278)

ECOG-PS, the Eastern Cooperative Oncology Group Performance Status; BMI, body mass index; ALT, Alanine transaminase; PHN, Post-herpetic neuralgia; CI, confidence interval

*P<0.05

anticholinergics [OR = 2.033, 95% CI = 1.150-3.594; P = 0.015], tramadol (OR = 0.488, 95% CI = 0.250-0.953; P =0.036), and chronic non-cancer pain (OR = 0.429, 95% CI = 0.197-0.937; P = 0.034) were identified as significant factors related to the effect of naldemedine. Accuracy was defined as the proportion of patients whose expected value was equal to the observed value (Table 2).

Table 2: Ordered logistic regression analysis results for variables extracted by forward selection (accuracy=120/210)

Variable	*P* value	Odds ratio	95% CI	
			Lower 95%	Upper 95%
Use of naldemedine within 2 days of opioid initiation	0.003*	0.346	0.173	0.693
Anticholinergics	0.015*	2.033	1.150	3.594
Tramadol	0.036*	0.488	0.250	0.953
Tapentadol	0.136	0.288	0.056	1.480
Chronic non-cancer pain	0.034*	0.429	0.197	0.937

CI, confidence interval
*P<0.05

There was a significant difference in the effect of naldemedine among opioids (P= 0.001). In the comparison of the effects of naldemedine among the different opioid administration groups, it was significantly more effective in the tramadol group than in the hydromorphone or oxycodone group (Fig.). Although not significant, there is a higher dosage of opioids (converted to morphine) in patients with cancer compared to the patients with non-cancer pain (Table 3). Among the opioids, patients with cancer pain used morphine, oxycodone, hydromorphone, and tapentadol more frequently, while non-cancer patients preferably received tramadol (Table 3).

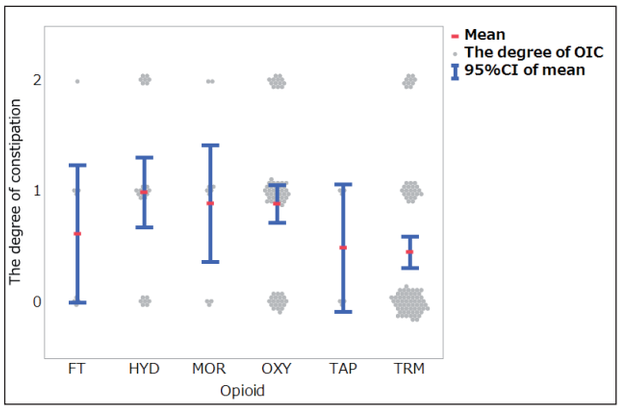

Fig.: Comparison of the degree of constipation among different opioids. CI, confidence interval; FT, fentanyl; HYD, hydromorphone; MOR, morphine; OXY, oxycodone; TAP, tapentadol; TRM, tramadol

Table 3: Comparison between patients with cancer and non-cancer pain as regards the dosage of opioids or type of opioid used

	Patients with cancer pain	Patients with non-cancer pain	*P* value
Daily dosage of opioid converted to morphine (mg), median (range)	30 (5-720)	20 (5-60)	0.18
Morphine, n (%)	11(7.2)	0	–
Oxycodone, n (%)	63 (41.2)	1(1.9)	<.0001*
Hydromorphone, n (%)	24 (15.7)	0	–
Fentanyl, n (%)	8 (5.2)	3(5.6)	0.93
Tapentadol, n (%)	6 (3.9)	0	–
Tramadol, n (%)	41(26.8)	50 (92.6)	<.0001*

3. Discussion

In this study, multivariate ordered logistic regression analysis showed that significant factors affecting the effect of naldemedine included the use of naldemedine within 2 days of opioid initiation, concomitant use of anticholinergics, tramadol, and chronic non-cancer pain. Besides, there was a significant difference in the effect of naldemedine among opioids and the differences between patients with cancer and non-cancer pain as regards the dosage of opioids or type of opioid used.

Naldemedine is a peripherally acting μ-opioid receptor antagonist that has recently been studied in randomized, controlled trials (RCTs) for OIC management (Hale et al. 2017; Katakami et al. 2017; Webster et al.2017, 2018). Therefore, it is clear from the mechanism of action that the use of naldemedine within 2 days of opioid initiation is effective. Administration of naldemedine at opioid initiation may also avoid the risk of developing opioid withdrawal symptoms due to the addition of naldemedine during opioid administration (Ishii et al. 2020). However, the guidelines for OIC suggest that classic laxatives should be used first, and if the effects are insufficient, use of novel constipation treatments or PAMORA is recommended (Crockett et al 2019; Garcia et al. 2018; Müller-Lissner et al. 2017). Further verification of the appropriate timing of naldemedine initiation is needed.

Anticholinergics are drugs that can cause constipation (Every-Palmer et al. 2017). Therefore, concomitant use of anticholinergics may attenuate the effects of naldemedine. Patients with pain are taking many anticholinergic drugs, such as sleeping pills and antipsychotics (Hwang et al.2016). Thus, clinicians need to be aware of this issue.

In addition, naldemedine was more effective in patients with chronic non-cancer pain than in patients with cancer pain. Since there was a relatively large number of patients with gastrointestinal cancer among the cancer patients, it was possible that some type of passage disorder other than that caused by opioids might be a factor causing constipation. On the other hand, although not significant, there was a higher dosage of opioid use in the oncological group than in the non-cancer group that affects the effectiveness of naldemedine. The same difference between the use of drugs in the two groups, the difference between the use of tramadol in the non-oncology compared to the oncology group also affects the effectiveness of naldemedine. Song et al. (2019) reported that adverse effects due to naldemedine are greater in cancer patients than in non-cancer patients (Song et al.2019). These may be the reasons that naldemedine is less effective in patients with cancer pain.

The present study also suggested that naldemedine was more effective for OIC in the tramadol group. Regarding opioid types, the degree of constipation was lower in the tramadol group than in the hydromorphone or oxycodone group. In addition, although not significant, the degree of constipation tended to be significantly lower in the fentanyl and tapentadol groups. Tramadol and fentanyl are considered to cause little constipation as an AE (Hadley et al. 2013; Meng et al. 2017; Radbruch et al. 2000). Thus, the frequency of constipation as an AE of each opioid appears to be correlated with the effect of naldemedine.

As for AEs of naldemedine, 1.3% patients discontinued naldemedine due to diarrhea. Although this result is less frequent than in clinical trials (Katakami et al. 2017; Webster et al. 2018), it is necessary to accumulate more cases in daily clinical practice.

The current study has some limitations. First, the retrospective design of the survey may have reduced the validity of the data gathered. Second, this study was conducted at a single institute. Therefore, the current results need to be supported in a prospective multicenter trial.

In conclusion, use of naldemedine within 2 days of opioid initiation, concomitant use of anticholinergics, tramadol, and chronic non-cancer pain were identified as significant factors affecting the effect of naldemedine on OIC. However, our results are preliminary and must be verified by further studies. Nevertheless, the identification of significant factors affecting the effect of naldemedine for OIC may assist to improve the QOL of patients receiving pain treatment using opioids.

4. Experimental

4.1. Patients and methods

A total of 230 patients who were prescribed naldemedine to alleviate OIC at our hospital between June 2017 and August 2019 were retrospectively analyzed. Patients who stopped naldemedine within 2 weeks of administration were excluded.

4.2. Statement of ethics

The Medical Ethics Review Committee at Kyoto Prefectural University of Medicine approved this study (approval no. ERB-C-1632). All procedures were performed in accordance with the ethical standards of the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine 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. Due to 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 ethical standards of the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine.

4.3. Extraction of variables

Variables associated with alleviation of OIC were extracted from clinical records and used for regression analysis. Variables extracted were factors potentially affecting OIC [sex, age, daily dosage of opioid converted to morphine (mg), use of naldemedine within 2 days of opioid initiation, opioid therapy period before naldemedine administration, brain tumor, use of routine laxatives before naldemedine administration, concomitant medication, opioid types, body mass index, height, weight, laboratory data and cancer pain or chronic non-cancer pain etc]. Naldemedine 0.2 mg was administered orally once a day.

The effect of naldemedine was evaluated two weeks after administration. Data on the effect of naldemedine was drawn from interviews with patients conducted by the treating physician, pharmacist and/or primary nurse during daily clinical practice. A retrospective nature of study failed to extract enough data on stool properties or number of spontaneous bowel movements (SBM). Thus, the effect of naldemedine was determined according to the degree of constipation.

The degree of constipation was categorized as grade 0 = not occurred (absent); grade 1 = occurred but did not require the additional laxatives and not feel discomfort or distress (mild or moderate); and grade 2 = occurred and require the additional laxatives and feel discomfort or distress (severe), with reference to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and previous research (Jensen et al.2018; Rodriguez et al.2007).

4.4. Statistical analysis

Variables were analyzed for multicollinearity (correlation coefficient $|r| \geq 0.7$), which can develop when correlations exist among variables, thereby resulting in building an inappropriate model.

First, univariate ordered logistic regression analyses were performed between the degree of constipation (objective variable) and each potential explanatory variable. A multivariate ordered logistic regression model was then built using the stepwise forward selection procedure among potential explanatory variables with a variable entry criterion of 0.2 and a variable retention criterion of 0.1. Ordered logistic regression analysis was used because the degree of constipation was assessed by means of a graded scale, and multiple factors potentially relevant as factors affecting the effect of naldemedine had to be evaluated simultaneously. Furthermore, whether there was a difference in the effect of naldemedine among opioids, and the differences between patients with cancer and non-cancer pain as regards the dosage of opioids or type of opioid used were analyzed using the Wilcoxon/Kruskal-Wallis test.

For all statistical analyses, values of $P < 0.05$ (2-tailed) were considered significant. All analyses were conducted using JMP ® version 14.3.0. (SAS Institute, Cary, NC, USA).

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Conflicts of interest: None declared.

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