Regular Article

Analysis of Predictive Factors for Diarrhea after the Administration of Naldemedine

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Naldemedine (NAL), a peripherally acting μ-opioid receptor antagonist, is effective for opioid-induced constipation (OIC). However, diarrhea is the most common adverse event. We investigated the incidence of NAL-induced diarrhea in patients who started NAL at Nagasaki University Hospital between June 2017 and March 2019. Predictors of NAL-induced diarrhea were analyzed using a multivariate logistic regression model. Two hundred and forty-two patients were included in the present study, and NAL-induced diarrhea was observed in 17.8% (43 patients). The results of multiple logistic regression analyses identified the administration of opioid analgesics for 8 d or longer before the initiation of NAL (odds ratio (OR): 2.20, 95% confidence interval (95% CI): 1.04–4.64, $p = 0.039$), the combination of a laxative (OR: 2.22, 95%CI: 1.03–4.81, $p = 0.042$), and the combination of CYP3A4 inhibitors (strong/moderate) (OR: 2.80, 95%CI: 1.02–7.67, $p = 0.045$) as risk factors. Therefore, the development of diarrhea needs to be considered in patients with these risk factors. Furthermore, diarrhea may be controlled by the initiation of NAL within 7 d of opioid analgesics and, where possible, the discontinuation of or change in the combination of moderate or strong CYP3A4 inhibitors.

Key words naldemedine; diarrhea; predictive factor; opioid analgesic; laxative; CYP3A4 inhibitor

INTRODUCTION

Opioid analgesics exert excellent effects on cancer pain or chronic pain by stimulating μ-opioid receptors in the central nervous system. However, major adverse events include nausea/vomiting, constipation, and drowsiness. Opioid-induced constipation (OIC) has been reported to occur in >40% of patients treated with opioid analgesics.[1–4] OIC is defined as changes from baseline bowel habits and defecation patterns, such as reduced bowel frequency, the development or worsening of straining, a feeling of incomplete defecation, or an awareness of patient distress associated with bowel habits after the initiation of opioids.[5] OIC is not tolerated as well as the other adverse events of nausea/vomiting and drowsiness, and OIC-induced abdominal discomfort and defecation symptoms persist throughout the administration of opioids.[6] OIC deteriorates QOL, such as vitality, physical functioning, mental state, mental health, general health, and social functioning. Adherence to opioid analgesics is also poor, which, in turn, results in inadequate pain management.[7] Therefore, the prevention and/or treatment of OIC are important.

The guidelines of the European Association for Palliative Care (EAPC),[8] European Society for Medical Oncology (ESMO),[9] National Comprehensive Cancer Network (NCCN),[10] and Japanese Society for Palliative Medicine[11] recommend osmotic and colonic laxatives as first-line treatments for OIC. Peripheral μ-opioid receptor antagonists (PAMORAs) are considered when OIC is refractory to laxatives. Although PAMORAs are effective against OIC, they cause gastrointestinal toxicity, such as diarrhea, abdominal pain, nausea, and vomiting. A meta-analysis revealed that the risk ratio for diarrhea was 2.07.[12]

All currently available PAMORAs, including naldemedine (NAL),[13] methylnaltrexone,[14] alvimopan,[15] naloxone,[16] and oral naloxone,[17] are effective treatments for OIC. A recent network meta-analysis showed that NAL and naloxone were the most effective for OIC.[18] NAL is the only PAMORA that is approved in Japan and is widely used for cancer or non-cancer patients with OIC. In a phase III randomized placebo-controlled trial, the frequency of spontaneous bowel movements was significantly increased in cancer patients receiving NAL.[13] Adverse events occurred in 44.3% of patients, with the most common adverse event being diarrhea (19.6%). The frequency of NAL-induced diarrhea was the highest on the first day of administration and gradually decreased after the second day.[19] If the incidence of diarrhea can be predicted, the safer administration of NAL may be possible. We previously reported that NAL-induced diarrhea significantly increased when opioid analgesics were administered for more than 8 d prior to the initiation of NAL.[20] Similar results also have been reported by other groups.[21,22]

On the other hand, NAL is mainly metabolized by CYP3A4. The concomitant use of CYP3A4 inhibitor and NAL increase blood concentration of NAL.[23] In addition, the incidence of NAL-induced diarrhea was higher in patients receiving 0.4 mg/d than in those receiving the approved dose of 0.2 mg/d, in phase II trial.[24,25] Therefore, CYP3A4 inhibitors may affect the incidence of NAL-induced diarrhea as a result of increasing blood levels of NAL. However, there are no reports the association between NAL-induced diarrhea and the

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concomitant use of CYP3A4 inhibitor. In the previous study, we reported that the duration of opioid analgesics was the predictive factor of NAL-induced diarrhea. Then, we extended the study period to increase the number of patients in order to improve the reliability of the information compared to previous reports,[20] and conducted retrospective study including the presence or absence of concomitant use of CYP3A4 inhibitors. As a result, we have found for the first time that the combinations of CYP3A4 inhibitors or laxatives are predictive factors for NAL-induced diarrhea.

MATERIALS AND METHODS

Patients The present study was performed in accordance with the Declaration of Helsinki (Ninth revision: Fortaleza, Brazil, 2013) and under approval by the Nagasaki University Ethics Committee (No. 20111603). The prevalence of OIC treated with NAL was investigated in patients hospitalized at Nagasaki University Hospital (Nagasaki, Japan) between June 2017 and March 2019. In total, 242 hospitalized patients were administered NAL for the first time. Exclusion criteria are as follows: (a) patients who were transferred or were not staying in the hospital less than 3 d from the initiation of NAL; (b) patients administered NAL in the outpatient clinic or another hospital; (c) patients for whom the starting date of opioids was not identified; and (d) patients who started tube feeding after the administration of NAL.

Data Collection and Assessment This was a retrospective study. Data were obtained on age, sex, weight, primary cancer, diseases impairing blood–brain barrier function, and the opioid dose used before the administration of NAL. Diseases impairing blood–brain barrier function were defined as metastatic brain tumors, AIDS-related dementia, multiple sclerosis, and Alzheimer's disease.[26] Opioid doses were converted to doses equivalent to oral morphine. The conversion ratios of opioid doses and oral morphine doses were as follows: 30 mg oral morphine = 20 mg oral oxycodone = 15 mg infused oxycodone = 0.3 mg fentanyl = 100 mg tapentadol = 6 mg oral hydromorphone = 1.2 mg infused hydromorphone = 150 mg tramadol = 3.5 mg oral methadone. Blood biomedical parameters included serum creatinine, the estimated glomerular filtration rate, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The following concomitant agents were investigated: laxatives; opioids; anti-cancer agents; CYP 3A4 inhibitors; CYP3A4 inducers; and P-glycoprotein inhibitors. CYP3A4 inhibitors/inducers were defined as drugs listed in the U.S. Food and Drug Administration (FDA) Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.[27] We investigated whether patients developed diarrhea within 3 d of the administration of NAL.

Statistical Analysis Differences between 2 groups were assessed using Fisher's exact test for categorical data and the Wilcoxon rank sum test for continuous data. Baseline characteristics were summarized with frequencies and percentages for categorical data and medians plus interquartile ranges for continuous data. Univariate logistic regression analyses were performed to evaluate the odds ratio (OR), 95% confidence intervals (CI), and p values of each potential risk factor for diarrhea from NAL. To adjust all analyses for confounders, potential confounding variables that significantly contributed to outcomes in the univariate logistic regression analysis ($p < 0.1$) were included in the multiple logistic regression analysis. All tests were two-sided. The level of significance was a p-value less than 0.05. Analyses were performed using JMP Pro version 15 (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Patient characteristics and treatment details were shown in Tables 1, 2. One hundred and sixty-three patients (67.4%) were men. In total, 40 (16.5%), 33 (13.6%), and 28 (11.6%) patients had head and neck, lung, and stomach/esophagus/small intestine cancers, respectively. Median age and weight were 66 years and 56.5 kg, respectively. The median period of opioid analgesics before the administration of NAL was 7 d. Furthermore, 20 mg was the median dose of opioid analgesics converted to oral morphine. The following drugs other than opioid analgesics were concomitantly administered: laxatives to 130 patients (53.7%), CYP3A4 inhibitors to 24 (9.9%), CYP3A4 inducers to 2 (0.8%), P-glycoprotein inhibitors to 7 (2.9%), and anticancer drugs to 107 (44.2%). Twenty-two (9.1%) patients received a moderate or strong CYP3A4 inhibitor combination, while 14 (5.8%) were using tube feeding.

The incidence of NAL-induced diarrhea was 17.8% (43 patients) (Table 3). The duration of opioid analgesics before the initiation of NAL was longer in the group with than without diarrhea (median 14 d *vs.* 6 d, $p = 0.002$). In addition, the number of patients who received the combination of CYP3A4 inhibitors (strong/moderate) and laxatives was significantly higher in the group with than without diarrhea ($p = 0.011$ and 0.035, respectively).

The results of the univariate logistic regression analysis

Table 1. Patient Characteristics

	$n = 242$
Sex (male)	163 (67.4%)
Age (years)	66 (59–74)
Weight (kg)	56.5 (47.1–62.5)
Laboratory data	
Serum creatinine (mg/dL)	0.81 (0.64–1.03)
AST (IU/L)	22 (16–38)
ALT (IU/L)	18 (12–30)
Estimated GFR (mL/min/1.73 m^2)	69.6 (53.3–85.9)
Main disease	
Head and neck cancer	40 (16.5%)
Lung cancer	33 (13.6%)
Gastric/esophageal/small intestine cancer	28 (11.6%)
Liver/biliary tract cancer	23 (9.5%)
Urinary cancer	20 (8.3%)
Gynecologic cancer	18 (7.4%)
Blood cancer	18 (7.4%)
Colorectal cancer	17 (7.0%)
Pancreatic cancer	15 (6.2%)
Malignant soft tissue tumor	13 (5.4%)
Breast cancer	7 (2.9%)
Skin cancer	2 (0.8%)
Cancer of unknown primary	2 (0.8%)
Others (including non-cancer)	6 (2.5%)
Diseases imparing blood–brain barrier function	6 (2.5%)

Categorical data are shown by frequencies and percentages, and continuous variables are represented by the median plus interquartile range. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GFR: Glomerular filtration rate.

Table 2. Usage of Concomitant Drugs and Tube Feeding

	Name of medicine	$n = 242$
Opioid analgesics (regular administration) (yes)		242 (100%)
	Oxycodone (*p.o.*)	106 (43.8%)
	Hydromorphine (*p.o.*)	36 (14.9%)
	Morphine (*p.o.*)	35 (14.5%)
	Tapentadol (*p.o.*)	20 (8.3%)
	Oxycodone (i.v.)	12 (5.0%)
	Tramadol (*p.o.*)	7 (2.9%)
	Fentanyl (patch)	4 (1.7%)
	Fentanyl (i.v.)	4 (1.7%)
	Oxycodone (*p.o.*)/morphine (*p.o.*)	4 (1.7%)
	Oxycodone (*p.o.*)/tramadol (*p.o.*)	3 (1.2%)
	Tapentadol (*p.o.*)/tramadol (*p.o.*)	3 (1.2%)
	Codeine phosphate (*p.o.*)	2 (0.8%)
	Morphine (*p.o.*)/codeine phosphate (*p.o.*)	2 (0.8%)
	Morphine (*p.o.*)/tramadol (*p.o.*)	1 (0.4%)
	Oxycodone (*p.o.*)/methadone (*p.o.*)	1 (0.4%)
	Oxycodone (*p.o.*)/fentanyl (patch)	1 (0.4%)
	Hydromorphine (i.v.)	1 (0.4%)
Dosage (oral morphine equivalent mg/d)		20 (15–40)
Administration period before the initiation of NAL (d)		7 (2–18)
Laxative (regular administration) (yes)		130 (53.7%)
(Including when used in combination)	Magnesium oxide	119 (49.2%)
	Sennoside	28 (11.6%)
	Lubiprostone	9 (3.7%)
	Linaclotide	8 (3.3%)
	Senna	4 (1.7%)
	Elobixibat	3 (1.2%)
CYP3A4 inhibitor (yes)		24 (9.9%)
Inhibition index		
Strong	Voriconazole	2 (0.8%)
	Clarithromycin	1 (0.4%)
	Clarithromycin + Voriconazole	1 (0.4%)
Moderate	Aprepitant	9 (3.7%)
	Fluconazole	7 (2.9%)
	Verapamil	1 (0.4%)
	Aprepitant + Fluconazole	1 (0.4%)
Weak	Cilostazol	1 (0.4%)
	Fosaprepitant	1 (0.4%)
CYP3A4 inducer (yes)		2 (0.8%)
Name of medicine	Phenytoin	2 (0.8%)
P-glycoprotein inhibitor (yes)		7 (2.9%)
Name of medicine	Carvedilol	4 (1.7%)
	Clarithromycin	2 (0.8%)
	Verapamil	1 (0.4%)
Anti-cancer agent (yes)		107 (44.2%)
Tube feeding (yes)		14 (5.8%)

Categorical data are shown by frequencies and percentages, and continuous variables are represented by the median plus interquartile range.

indicated that lung cancer, the administration of opioid analgesics for 8 d or longer before the initiation of NAL, the combination of laxatives, CYP3A4 inhibitors (strong/moderate), and P-glycoprotein inhibitors, and the use of tube feeding were candidate risk factors for diarrhea. The results of multiple logistic regression analyses identified the administration of opioid analgesics for 8 d or longer before the initiation of NAL (OR): 2.20, 95% CI: 1.04–4.64, $p = 0.039$) and the combination of laxatives (OR: 2.22, 95%CI: 1.03–4.81, $p = 0.042$) and CYP3A4 inhibitors (strong/moderate) (OR: 2.80, 95%CI: 1.02–7.67, $p = 0.045$) as risk factors for diarrhea (Table 4). The frequency of NAL-induced diarrhea was calculated in patients who received opioid analgesics for 8 d or longer, laxatives, and CYP3A4 inhibitors. The incidence of NAL-induced diarrhea was 7.1, 12.8, 30.8, and 37.5% when there were 0, 1, 2, and 3 predictors, respectively (Fig. 1). Details on the combination of predictors are shown in Supplementary Table 1.

DISCUSSION

To the best of our knowledge, this is the first study to report the combination of CYP3A4 inhibitors or laxatives are risk

Table 3. Comparison of Patient Characteristic in the with Diarrhea Group and without Group

	With diarrhea ($n = 43$)	Without diarrhea ($n = 199$)	p-Value
Patient characteristics			
Sex (male)	27 (62.8%)	136 (68.3%)	0.479[a)]
Age (years)	68 (59–76)	66 (58–74)	0.289[b)]
Weight (kg)	56.0 (45.4–61.3)	56.5 (47.9–63.5)	0.208[b)]
Laboratory data			
Serum creatinine (mg/dL)	0.79 (0.64–1.16)	0.81 (0.64–1.00)	0.346[b)]
AST (IU/L)	26 (18–36)	22 (16–38)	0.445[b)]
ALT (IU/L)	20 (14–27)	18 (12–31)	0.506[b)]
Estimated GFR (mL/min/1.73 m^2)	68.2 (43.1–81.7)	69.6 (55.0–86.5)	0.123[b)]
Main disease			
Head and neck cancer	7 (16.3%)	33 (16.6%)	1.000[a)]
Lung cancer	2 (4.7%)	31 (15.6%)	0.083[a)]
Gastric/esophageal/small intestine cancer	5 (11.6%)	23 (11.6%)	1.000[a)]
Liver/biliary tract cancer	2 (4.7%)	21 (10.6%)	0.388[a)]
Urinary cancer	4 (9.3%)	16 (8.0%)	0.762[a)]
Gynecologic cancer	5 (11.6%)	13 (6.5%)	0.331[a)]
Blood cancer	4 (9.3%)	14 (7.0%)	0.536[a)]
Colorectal cancer	3 (7.0%)	14 (7.0%)	1.000[a)]
Pancreatic cancer	4 (9.3%)	11 (5.5%)	0.314[a)]
Malignant soft tissue tumor	1 (2.3%)	12 (6.0%)	0.474[a)]
Breast cancer	2 (4.7%)	5 (2.5%)	0.611[a)]
Skin cancer	1 (2.3%)	1 (0.5%)	0.324[a)]
Cancer of unknown primary	1 (2.3%)	1 (0.5%)	0.324[a)]
Others (including non-cancers)	2 (4.7%)	4 (2.0%)	0.289[a)]
Diseases impairing blood–brain barrier function	1 (2.3%)	5 (2.5%)	1.000[a)]
Concomitant drugs/tube feeding			
Opioid analgesics (regular administration)			
Dosage (oral morphine equivalent mg/d)	20 (15–45)	23 (15–40)	0.667[b)]
Administration period before the initiation of NAL (d)	14 (6–31)	6 (2–17)	0.002[b)]
Administration period before the initiation of NAL (>8 d)	29 (67.4%)	85 (42.7%)	0.004[a)]
Laxatives (regular administration) (yes)	31 (72.1%)	99 (49.8%)	0.011[a)]
CYP3A4 inhibitor			
Strong/moderate/weak (yes)	9 (20.9%)	19 (9.5%)	0.061[a)]
Strong/moderate (yes)	8 (18.6%)	14 (7.0%)	0.035[a)]
CYP3A4 inducer (yes)	0 (0%)	2 (1.0%)	1.000[a)]
P-glycoprotein inhibitor (yes)	3 (7.0%)	4 (2.0%)	0.109[a)]
Anti-cancer agent (yes)	21 (48.8%)	86 (43.2%)	0.504[a)]
Tube feeding (yes)	5 (11.6%)	9 (4.5%)	0.081[a)]

Categorical data are shown by frequencies and percentages, and continuous variables are represented by the median plus interquartile range. *a*) Fisher's exact test, *b*) the Wilcoxon rank sum test. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GFR: Glomerular filtration rate.

factors for NAL-induced diarrhea. The multivariate analysis in the present study identified the combination of laxatives or CYP3A4 inhibitors (strong/medium) in addition to the duration of opioid analgesics as novel predictors of NAL-induced diarrhea. We previously reported that eight days or longer of opioid analgesics before the initiation of NAL was identified as an independent predictor of NAL-induced diarrhea. On the other hand, 12.5% of patients administered opioid analgesics within 7 d developed NAL-induced diarrhea in the previous study.[20)] The incidence of diarrhea was 7.1% (5/70) in patients who did not have any of the predictors. The three predictors identified in the present study help to prevent NAL-induced diarrhea. The incidence of diarrhea in patients with two predictive factors was 30.8%, which was approximately four-fold higher than that in patients without risk factors. Seventy out of 79 patients had received opioid analgesics for 8 d or longer before the initiation of NAL and laxatives, and this value reflects the concomitant administration of opioid analgesics and laxatives. Since the incidence of diarrhea increase with a larger number of predictors, patients with a large number of predictors need to be more carefully observed.

NAL antagonizes the μ opioid receptor in the gastrointestinal tract and attenuates OIC. The combined use of NAL and laxatives exerted additive effects on OIC and promoted excessive defecation. A previous study reported that the discontinuation of other laxatives attenuated diarrhea in 92% of patients when diarrhea developed in those who combined NAL with other laxatives.[21)] These findings are consistent with the present results showing that the combination of laxatives is a predictor of NAL-induced diarrhea.

NAL is mainly metabolized by CYP3A4. A phase I trial on healthy individuals showed that the combination of itraconazole and fluconazole, which are strong and moderate CYP3A4 inhibitors, respectively, increased the area under

Table 4. Logistic Regression Analysis for Incidence of Naldemedine-Induced Diarrhea

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Sex (female *vs.* male)	1.28 (0.64–2.54)	0.482		
Age (per 10 years)	1.19 (0.91–1.60)	0.228		
Weight (per 10 kg)	0.83 (0.62–1.12)	0.229		
Laboratory data				
Serum creatinine (per 0.1 mg/dL)	1.08 (0.99–1.03)	0.104		
AST (per 10 IU/L)	1.00 (0.92–1.06)	0.925		
ALT (per 10 IU/L)	1.00 (0.87–1.11)	0.974		
Estimated GFR (per 10 mL/min/1.73 m^2)	0.90 (0.79–1.03)	0.124		
Main disease				
Head and neck cancer	0.98 (0.40–2.39)	0.961		
Lung cancer	0.26 (0.06–1.15)	0.076	0.25 (0.06–1.14)	0.073
Gastric/esophageal/small intestine cancer	1.01 (0.32–2.63)	0.990		
Liver/biliary tract cancer	0.41 (0.07–1.49)	0.196		
Urinary cancer	1.17 (0.37–3.70)	0.785		
Gynecologic cancer	1.88 (0.63–5.59)	0.255		
Blood cancer	1.36 (0.42–4.34)	0.609		
Colorectal cancer	0.99 (0.22–3.21)	0.989		
Pancreatic cancer	1.75 (0.53–5.79)	0.357		
Malignant soft tissue tumor	0.37 (0.02–1.96)	0.283		
Breast cancer	1.89 (0.35–10.10)	0.455		
Skin cancer	4.71 (0.29–76.89)	0.276		
Cancer of unknown primary	4.71 (0.29–76.89)	0.276		
Others (including non-cancers)	2.38 (0.42–13.42)	0.327		
Diseases impairing blood–brain barrier function (yes *vs.* no)	0.92 (0.11–8.11)	0.943		
Opioid analgesics (regular administration)				
Dosage (per oral morphine equivalent 10 mg/d)	0.96 (0.84–1.02)	0.494		
Administration period before the initiation of NAL (>8 d *vs.* 1–7 d)	2.78 (1.38–5.58)	0.004	2.20 (1.04–4.64)	0.039
Laxatives (regular administration) (yes *vs.* no)	2.61 (1.27–5.37)	0.009	2.22 (1.03–4.81)	0.042
CYP3A4 inhibitor (Strong/Medium *vs.* Weak/Nothing)	3.02 (1.18–7.74)	0.021	2.80 (1.02–7.67)	0.045
CYP3A4 inducer (yes *vs.* no)	—	—		
P-glycoprotein inhibitor (yes *vs.* no)	3.66 (0.79–16.97)	0.098	2.85 (0.52–15.52)	0.225
Anti-cancer agent (yes *vs.* no)	1.25 (0.65–2.43)	0.501		
Tube feeding (yes *vs.* no)	2.78 (0.88–8.75)	0.081	2.51 (0.73–8.62)	0.143

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GFR: Glomerular filtration rate.

the curve (*AUC*) by 2.91- and 1.90-fold, respectively.[23] We hypothesized that the combination of CYP3A4 inhibitors contributed to increase in the incidence of diarrhea by elevating the exposure level of NAL. In a phase I study, there were no NAL-related adverse events.[23] The healthy individuals were not administered opioid analgesics in the present study, so we believe that they don't have developed withdrawal symptoms. NAL is also a substrate for P-glycoprotein. The combination of cyclosporine, a P-glycoprotein inhibitor, increased the *AUC* of NAL by 1.78-fold.[23] However, the combination of P-glycoprotein did not correlate with NAL-induced diarrhea for the results of the multivariate analysis. In the present study, only 7 patients received the combination of P-glycoprotein (2.9%), and, thus, the detection power has been insufficient. Concomitant use with p-glycoprotein inhibitors needs to be confirmed by the accumulation of more cases.

The incidence of diarrhea in phase III clinical trials was previously reported to range between 18.3 and 40.0%.[13,28] However, the incidence of diarrhea in the present study was 17.8% (43/242), which was equal to or slightly lower than that reported in clinical trials. In previous clinical trials, patients who had been receiving opioid analgesics for at least 14 d were eligible to participate. Furthermore, between 74.2 and 90% of patients had been administered laxatives before the initiation of NAL. Therefore, the patient population in clinical trials was more likely to develop diarrhea than that in the present study. Furthermore, a subgroup analysis showed that diarrhea developed in 30.7% (24/78) of patients who used opioid analgesics and laxatives for 8 d or longer, which was similar to that in phase III clinical trials[13,28] (Supplementary Table 1).

The present study had several limitations. Outpatients and patients who did not have a medical record of survey contents were excluded from the present study. Furthermore, the present study was conducted at a single hospital. Therefore, there have been selection biases. In addition, this was a retrospective study. The incidence of diarrhea was investigated from medical records completed by doctors or nurses; therefore, some records have been missing. Moreover, several factors were not investigated due to the lack of medical records. The performance status, physical activity, and dietary intake may affect the incidence of diarrhea. Multicenter prospective studies are needed to resolve these limitations. Although the analysis of the therapeutic effect of NAL is also as important as any other laxative,[29] we did not investigate the therapeutic

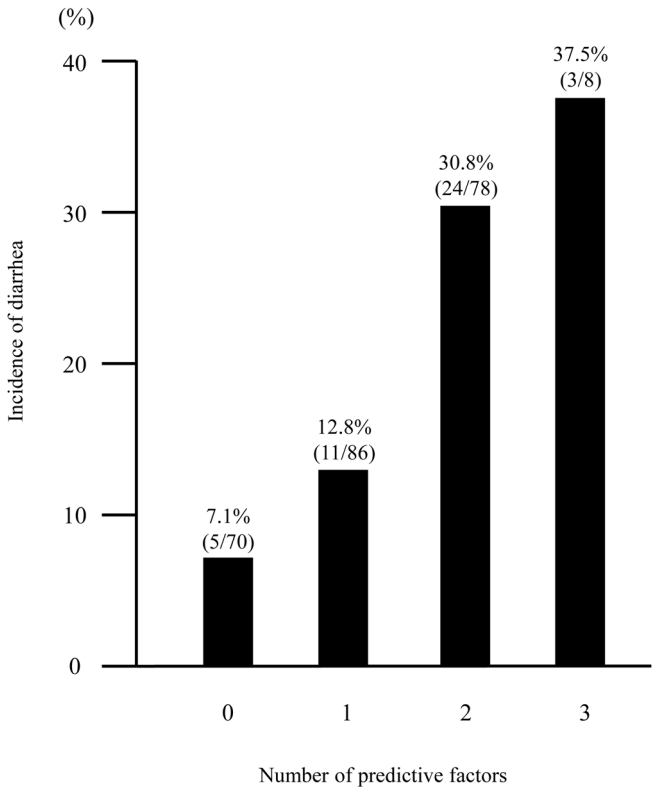

Fig. 1. The Combination of Opioid Analgesics for More than 8 d, Laxatives and CYP3A4 Inhibitors Are Predictors of Naldemedine-Induced Diarrhea

Patients with higher number of these predictors are more likely to develop naldemedine-induced diarrhea.

effect due to focus on adverse events in this paper. Further research is needed on the association between the therapeutic effect and adverse events.

In conclusion, opioid analgesics used for more than 8 d or in combination with laxatives or CYP3A4 inhibitors (strong/moderate) were considered to increase the risk of NAL-induced diarrhea. The development of diarrhea needs to be considered prior to the administration of NAL to patients with these predictors. In addition, diarrhea may be avoided by using opioid analgesics within 7 d of the initiation of NAL and, if possible, discontinuing or changing the combination of moderate or strong CYP3A4 inhibitors. The present results provide useful basic information for the proper use of NAL; however, further studies are warranted.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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