Impacts of genetic polymorphisms and cancer cachexia on naldemedine pharmacokinetics and bowel movements in patients receiving opioid analgesics

Received: 8 September 2023 | Accepted: 14 December 2023

DOI: 10.1111/fcp.12976

ORIGINAL ARTICLE

Fundamental & Clinical Pharmacology | WILEY

Impacts of genetic polymorphisms and cancer cachexia on naldemedine pharmacokinetics and bowel movements in patients receiving opioid analgesics

Emi Nakatsugawa[1] | **Takafumi Naito**[1,2] | **Kaito Shibata**[1,2] | **Ryo Kitajima**[3] | **Junichi Kawakami**[1]

[1]Department of Hospital Pharmacy, Hamamatsu University School of Medicine, Hamamatsu, Japan

[2]Department of Pharmacy, Shinshu University Hospital, Matsumoto, Japan

[3]Division of Palliative Care Center, Hamamatsu University Hospital, Hamamatsu, Japan

Correspondence
Takafumi Naito, Department of Pharmacy, Shinshu University Hospital, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan.
Email: naitou@shinshu-u.ac.jp

Funding information
JSPS KAKENHI, Grant/Award Numbers: 21H04204, 21K06664, 22H04287

Abstract

Background/Objectives: Clinical responses to naldemedine vary between individuals with advanced cancer. This is a prospective, single-center, observational study aimed to evaluate the influence of genetic polymorphisms and cachexia status on plasma naldemedine and clinical responses.

Methods: Forty-eight patients being treated with naldemedine for opioid-induced constipation under treatment of cancer pain were enrolled. Plasma naldemedine concentrations were determined on the fourth day or later after administration of naldemedine, and the associations with genotypes, cachexia status, and clinical responses were assessed.

Results: Cancer patients exhibited a large variation in the plasma naldemedine concentrations, and it was correlated with serum total protein level. Patients who were homozygous *CYP3A5*3* had a higher plasma concentration of naldemedine than those with the **1* allele. ABCB1 genotypes tested in this study were not associated with plasma naldemedine. A negative correlation was observed between the plasma naldemedine concentration and 4β-hydroxycholesterol level. The plasma naldemedine concentration was lower in patients with refractory cachexia than in those with precachexia and cachexia. While serum levels of interleukin-6 (IL-6) and acute-phase proteins were higher in patients with refractory cachexia, they were not associated with plasma naldemedine. A higher plasma concentration of naldemedine, *CYP3A5*3/*3*, and an earlier naldemedine administration after starting opioid analgesics were related to improvement of bowel movements.

Conclusion: Plasma naldemedine increased under deficient activity of CYP3A5 in cancer patients. Cachectic patients with a higher serum IL-6 had a lower plasma naldemedine. Plasma naldemedine, related to CYP3A5 genotype, and the initiation timing of naldemedine were associated with improved bowel movements.

Abbreviations: 4β-OHC, 4β-hydroxycholesterol; 4β-OHC/TC, serum total cholesterol normalized plasma 4β-hydroxycholesterol; ABCB1, ATP-binding cassette subfamily B member 1; AGP, α1-acid glycoprotein; COMT, catechol-*O*-methyltransferase; CRP, C-reactive protein; CYP, cytochrome P450; ELISA, enzyme-linked immunosorbent assay; GPS, Glasgow prognostic score; IL-6, interleukin-6; IQR, interquartile range; IS, internal standard; LC–MS/MS, liquid chromatograph coupled to a tandem mass spectrometer; LLOQ, lower limit of quantification; OIC, opioid-induced constipation; OPRM1, μ1-opioid receptor; P-gp, p-glycoprotein; SBM, spontaneous bowel movement.

KEYWORDS
cachexia, genetic polymorphism, naldemedine, opioid-induced constipation, pharmacokinetics

1 | INTRODUCTION

Opioid-induced constipation (OIC) is not a self-limiting adverse effect of opioid therapy, and more than 40% of patients reported experiencing OIC [1–3]. Treatment of OIC is necessary to continue acceptable opioid therapy with optimal pain relief [4]. Naldemedine, an opioid receptor μ1 (OPRM1) antagonist, is commonly used for constipation refractory to normal laxatives. Approximately 40% of patients developed diarrhea or loose stools with a therapeutic dose of naldemedine [5]. Although naldemedine is not recognized as a possible factor of opioid withdrawal because of its poor central distribution, its product information warns about opioid withdrawal in patients with a brain disorder [6–8]. The associations of naldemedine pharmacokinetics with its clinical responses have not been fully investigated in cancer patients.

The oral bioavailability of naldemedine is approximately 30%, and its main elimination pathway is metabolic inactivation by CYP3A [6, 8]. Naldemedine pharmacokinetics and its association with CYP3A activity still need to be clarified in cancer patients. CYP3A activity varies between individuals, and plasma 4β-hydroxycholesterol (4β-OHC) is used as an endogenous marker of total CYP3A activity [9]. Not only CYP3A4 activity but also CYP3A5 genotype is related to the production of 4β-OHC [10]. Homozygous *CYP3A5*3* patients were reported to have a low plasma 4β-OHC [11]. Naldemedine pharmacokinetics have not been characterized in terms of CYP3A activity using plasma 4β-OHC and CYP3A5 genotype.

Naldemedine is a substrate of P-glycoprotein (P-gp) encoded by ABCB1, regulating the intestinal absorption of drugs. Co-administration of potent P-gp inhibitors such as cyclosporine has been shown to increase naldemedine exposure in healthy subjects [12]. P-gp also restricts the entry of drugs into the central nervous system at the blood brain barrier [13]. The contribution of P-gp to restricted distribution of naldemedine into the brain remains to be clarified. ABCB1 has several genetic variants affecting its transport activity and drug clinical responses [14, 15]. The activities of OPRM1 and catechol-*O*-methyltransferase (COMT), which have meaningful genetic mutations, also potentially altered the clinical responses to opioid analgesics [16, 17]. The associations of their genotypes with the clinical responses to naldemedine have not been fully investigated in cancer patients receiving opioid analgesics.

Naldemedine is mostly administered to advanced cancer patients in Japan. Cancer cachexia reduces the activity of drug-metabolizing enzymes and transporters [18]. The onset of cachexia is associated with the overproduction of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α [19]. These cytokines predominantly downregulate the expression of CYP3A4. Cachectic cancer patients with elevated serum IL-6 were reported to have a higher plasma concentration of CYP3A4 substrates [20]. The elevated IL-6 potentially leads to changes in blood brain barrier permeability [21]. The associations of naldemedine pharmacokinetics with cachexia status have not been evaluated in cancer patients.

Patients with genetic polymorphisms or cancer cachexia are at a potential risk of adverse effects due to increased plasma naldemedine, while plasma naldemedine and its clinical response have never been investigated in terms of genotypes and cachexia progression. We hypothesized that plasma naldemedine increased in patients (1) with genotypes of CYP3A5 and ABCB1 and (2) with cachectic status. This is the first report that evaluated the influence of genetic polymorphisms and cancer cachexia on plasma naldemedine. Since dose-dependent efficacy of naldemedine was reported [22], the associations of plasma naldemedine with clinical responses were assessed as secondary objectives.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics

This prospective, single-center observational study was conducted to evaluate the influence of genetic polymorphisms and cancer cachexia on plasma naldemedine as the primary objective. The secondary objective is to assess the associations of plasma naldemedine with clinical responses. This study was conducted in accordance with the Declaration of Helsinki and its amendments. The protocol was registered with the University Hospital Medical Information Network (000042675) and was approved by the Ethics Committee of Hamamatsu University School of Medicine (20-261). All patients were informed about the study and consented in writing prior to participation.

2.2 | Patients and blood sampling

This study was conducted in patients admitted at Hamamatsu University Hospital from December 2019 to November 2022. The prescription history of

naldemedine was checked once a week using dispensing system (YUNiCOM-GX, Yuyama MFG Co. Ltd., Osaka, Japan). Among them, cancer patients who were taking opioid analgesics were selected, and remaining blood samples of medical examinations were collected. A total of 58 patients administered 0.2 mg of oral naldemedine (Shionogi & Co., Ltd., Tokyo, Japan) once daily after breakfast for at least four consecutive days for constipation under treatment of opioid analgesics for cancer pain were recruited. Exclusion criteria were as follows: patients who (1) were receiving weak opioids such as codeine and tramadol; (2) had liver dysfunction (serum total bilirubin > 2.0 mg/dL); (3) had decreased renal function (serum creatinine > 2.0 mg/dL); (4) were being co-treated with any strong CYP3A4 inducers or inhibitors such as rifampicin, ritonavir, azole antifungals, and clarithromycin [23]; (5) were being co-treated with potent P-gp inhibitors including cyclosporine, amiodarone, and verapamil [24]; (6) had a brain tumor or metastasis based on medical history; and (7) were suspected of poor drug adherence based on medical records. Ten patients were excluded and 48 were enrolled in the present study. The blood samples were collected into tubes containing EDTA dipotassium salt 24 h after dosing on the fourth day or later after starting the medication when the concentration was presumed to be at steady state.

2.3 | Determination of plasma naldemedine

Methanol (800 μL) containing perampanel as an internal standard (IS) was added to 200 μL of EDTA treated-plasma. The mixed solutions were centrifuged, and aliquots of the methanol extract were dried using a rotary vacuum evaporator. The residues were reconstituted with the mobile phase, and 5 μL aliquots were injected into a liquid chromatograph coupled to a tandem mass spectrometer (LC–MS/MS) system (Nexera and LCMS-8050, Shimadzu Corporation, Kyoto, Japan). Analytes were separated using a 2.6-μm particle size octadecyl silyl column (Kinetex C18, 100 mm length × 2.1 mm inner diameter, Phenomenex Inc., Torrance, CA, USA) with a guard column (SecurityGuard Ultra Cartridge, Phenomenex Inc.) and isocratic elution of 50% methanol containing 0.05% formic acid in water at a flow rate of 0.2 mL/min. The ion transitions were scanned in the positive ionization multiple reaction monitoring mode for naldemedine, $m/z = 571.65/369.10$, and for IS, 350.40/219.15. The linearity ($r > 0.999$) of the calibration curve was observed over the range of 0.125–5 ng/mL. The lower limit of quantification (LLOQ) of naldemedine was 0.125 ng/mL. The intra-day and inter-day accuracy of naldemedine was 98.9–105.6%, while their imprecision was 2.3–9.1%.

2.4 | Measurement of plasma 4β-hydroxycholesterol

The plasma level of 4β-OHC was quantified by LC–MS/MS using a modified method [11]. Analytes were separated using a 3-μm particle size octadecyl silyl column (TSKgel ODS-100Z, 75 mm length × 2.0 mm inner diameter, Tosoh, Tokyo, Japan) and isocratic elution of 90% acetonitrile in water at a flow rate of 0.2 mL/min. Using an atmospheric pressure chemical ionization probe, the ion transitions were scanned in the positive ionization multiple reaction monitoring mode for 4β-OHC, $m/z = 385.01/109.00$, and d7-4β-OHC, 392.30/97.30. The linearity ($r = 0.998$) of the calibration curve was observed over the range of 6.25–200 ng/mL. The LLOQ of 4β-OHC was 6.25 ng/mL. The intra-day and inter-day accuracy of 4β-OHC was 96.7–106.2%, while their imprecision was 3.2–11.3%. Serum total cholesterol was determined using an enzyme assay (Cholesterol E-Test Wako, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). The LLOQ for serum total cholesterol was 2.2 mg/dL.

2.5 | Genotyping

Genomic DNA was extracted from whole blood cell using DNA Extractor WB Kit (FUJIFILM Wako Pure Chemical Corporation) and stored at −20°C. The single nucleotide polymorphisms of *CYP3A5* c.6986A > G (rs776746), *ABCB1* c.1236C > T (rs1128503), c.2677G > T (rs2032582), c.3435C > T (rs1045642), *OPRM1* c.118A > G (rs1799971), and *COMT* p.Val158Met (rs4680) were identified using a real-time polymerase chain reaction with TaqMan probes on StepOne Plus Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA). Genotyping was conducted in multiple batches at an experimental laboratory in Hamamatsu University Hospital. All the frequencies of genotypes were in Hardy–Weinberg equilibrium ($P > 0.05$) using the chi-squared test (*ABCB1* C1236T, G2677T, C3435T, and *OPRM1* A118G) and the Fisher's exact test (*CYP3A5* A6986G and *COMT* Val158Met). The patients with *CYP3A5*1/*1* or **1/*3* were classified into one group of patients with *CYP3A5*1* allele in the analysis. The homozygous variants of the 3 ABCB1 genotypes (1236TT-2677TT-3435TT) were defined as *ABCB1* triple TT diplotype. Patients were divided into two groups (wild type and mutant) in the OPRM1 and COMT analyses.

2.6 | Evaluation of cancer cachexia

Serum levels of IL-6 and α1-acid glycoprotein (AGP) were measured using enzyme-linked immunosorbent assay (ELISA) kits from BioLegend Inc. (San Diego,

CA, USA) and R&D Systems, Inc. (Minneapolis, MN, USA), respectively. The LLOQ for serum IL-6 and AGP were 1.6 pg/mL and 3.13 mg/dL, respectively. The serum level of C-reactive protein (CRP) was obtained from the electronic medical records of each patient at the day of blood sampling used for the quantification of plasma naldemedine. The degree of cancer cachexia was measured using the guideline recommended by EPCRC and Glasgow prognostic score (GPS) [25, 26].

2.7 | Outcomes

The outcome of this study is plasma naldemedine concentration and bowel movements. Bowel movements were assessed by three ways: (1) spontaneous bowel movement (SBM) responders (defined as a patient with an SBM per week frequency of at least 3 and an average increase in frequency of SBMs per week from baseline by at least 1) [5]; (2) SBM during the 1 week period around blood sampling (patients were divided into two groups according to the SBM in the week [<4 or ≥4 times]); and (3) the incidence of diarrhea. Twelve patients were excluded from the analysis of SBM responders due to the lack of baseline data. Diarrhea was evaluated by CTCAE 5.0 and the Bristol scale. Patient data on the occurrence of diarrhea and opioid withdrawal syndrome were collected for 1 week around the time of blood sampling from their electronic medical records. Common biochemical test values were obtained from the electronic medical records of each patient at the day of blood sampling. Bowel movements were recorded by medical staff independent of research team.

2.8 | Statistical analysis

The correlations between plasma naldemedine and continuous parameters (biochemical test values, IL-6, and AGP) were evaluated using the non-parametric Spearman test, and its rank correlation coefficient was described as r_s. The difference in plasma naldemedine between genotypes, cachexia status, concomitant drugs, and the patients with and without clinical response were compared using the Kruskal–Wallis test and the Mann–Whitney *U* test. The Mann–Whitney *U* test is also used to compare differences in 4β-OHC/TC by *CYP3A5*3* and in inflammatory marker levels by cachexia status. Univariate logistic regression was performed to investigate associations of SBM responder with explanatory valuables: plasma naldemedine, *CYP3A5*3/*3*, *OPRM1* c.118A > G, *COMT* p.-Val158Met, date of starting naldemedine administration, and concomitant other laxatives, GPS 2, and concomitant antacids. Multiple logistic regression (forced entry model) was conducted to evaluate the effect of plasma naldemedine on the clinical response adjusted for *OPRM1* c.118A > G, *COMT* p.-Val158Met, and date of starting naldemedine administration. The following factors (*CYP3A5*3/*3*, Co-administration of other laxatives, GPS 2, and Concomitant antacids) were excluded from the multivariate analysis because these factors were directly related to plasma naldemedine concentration. In order to reveal the contribution of antacids and cachexia on plasma naldemedine and SBM response, plasma naldemedine and SBM responder rates were evaluated in four groups as follows: (1) GPS 2 with antacids; (2) GPS 0–1 with antacids; (3) GPS 2 without antacids; and (4) GPS 0–1 without antacids. Receiver operating characteristic curve analysis was conducted to determine the cut-off value of plasma naldemedine for SBM with optimum sensitivity and specificity. A two-sided P value < 0.05 was considered statistically significant. All statistics were analyzed using IBM SPSS Statistics, ver. 26 (IBM Japan Ltd., Tokyo). Target sample sizes for correlation analysis is 26 according to statistical power analysis with effect size of 0.5, statistical power of 0.8, and a significance level of 0.05 using G power ver. 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). All the analyses included 48 patients enrolled in this study, with the exception of the SBM responder analysis. The SBM responder analysis was performed in 36 patients, excluding 12 patients for whom SBM response was difficult to be detected due to lack of baseline bowel movements data.

3 | RESULTS

3.1 | Patient characteristics

This study population (median age, 71 years) had low serum levels of albumin (median, 31 g/L) and total protein (median, 62 g/L) and a low body mass index (median, 20.4) (Table 1). The patients were suffering from the following; head and neck cancer ($n = 12$), lung cancer ($n = 10$), colorectal cancer ($n = 3$), esophageal cancer ($n = 3$), ovarian cancer ($n = 3$), cancer of the renal pelvis and ureter ($n = 3$), and other types of cancer ($n = 14$). Thirty patients were co-administered laxatives such as magnesium oxide ($n = 21$), linaclotide ($n = 5$), lubiprostone ($n = 5$), and elobixibat ($n = 4$). Nine of these patients were taking two laxatives in addition to naldemedine.

3.2 | Interindividual variation in plasma naldemedine

The absolute concentration of plasma naldemedine ranged from 125 pg/mL to 4.38 ng/mL (median, 1.12 ng/mL). The median and interquartile range (IQR)

TABLE 1 Characteristics of the study patients.

(A) Physical status and biochemical tests	
Gender, male/female, *n*	37/11
Age, years	71 (61–74)
Body weight, kg	54 (49–61)
Body mass index	20.4 (18.7–22.6)
Serum albumin, g/L	31 (28–35)
Serum total protein, g/L	62 (58–67)
Serum total bilirubin, mg/dL	0.5 (0.4–0.7)
Serum aspartate aminotransferase, U/L	25 (17–38)
Serum alanine aminotransferase, U/L	21 (11–36)
Serum alkaline phosphatase, U/L	109 (86–177)
Serum creatinine, mg/dL	0.8 (0.6–1.0)
Serum blood urea nitrogen, mg/dL	16.6 (12.0–22.9)
(B) Cancer and treatment-related status and genotype	
Stages of cancer, ≤2/3/4	5/7/36
Serum C-reactive protein, mg/dL	3.90 (1.75–8.67)
Concomitant baseline opioid analgesics, *n*	
Morphine/oxycodone/fentanyl/others	13/28/4/3
Oral morphine equivalent dose of opioids, mg	45 (20–60)
Duration of naldemedine administration, <14/14–28/>28 days, *n*	28/7/13
Date of starting naldemedine administration, *n*	
Within 2 days after opioid initiation	28
3 days or later after opioid initiation	20
Number of co-administrations of other laxatives, 0/1/2	18/21/9
Concomitant drugs, *n*	
Aprepitant/Antacids (PPI or H2RA)/Glucocorticoid	7/27/17
Distribution of genetic polymorphisms, *n*	
CYP3A5, **1/*1*, **1/*3*, **3/*3*	1, 16, 31
ABCB1, 1236CC, 1236CT, 1236TT	6, 25, 17
ABCB1, 2677GG, 2677GT, 2677TT	17, 17, 14
ABCB1, 3435CC, 3435CT, 3435TT	18, 21, 9
OPRM1, 118AA, 118AG, 118GG	20, 20, 8
COMT, 158Val/Val, 158Val/Met, 158Met/Met	23, 19, 6

Note: Biochemical test values were obtained on the day of blood sampling. Data are expressed as the median and interquartile range in parentheses. Abbreviations: COMT, catechol-*O*-methyltransferase; H2RA, histamine H2-receptor antagonist; OPRM1, μ1-opioid receptor; PPI, proton pump inhibitor.

of dose and body weight-adjusted concentrations were 320 and 136–559 ng/mL per mg/kg, respectively. The serum total protein level was correlated with the plasma naldemedine concentration ($r_s = 0.353$, $P = 0.014$). No difference was observed between the plasma naldemedine concentration and other major biochemical test values including serum albumin ($r_s = 0.201$, $P = 0.171$) (Table S1). The patients with concomitant use of aprepitant showed a higher plasma naldemedine concentration ($P = 0.042$). Concomitant use of antacids (a proton pump inhibitor or histamine H2 receptor antagonist) and magnesium oxide decreased plasma naldemedine concentration ($P = 0.028$ and $P = 0.017$, respectively).

3.3 | Relationship with CYP3A5 and ABCB1 genotypes

Genotyping was attempted at 48 patients enrolled in this study, and no genotyping error was observed. The plasma concentration of naldemedine was higher in the patients with *CYP3A5*3/*3* than in those with **1* allele ($P = 0.038$) (Figure 1). Significant differences were not observed in the plasma naldemedine concentration between the *ABCB1* C1236T, G2677T, and C3435T genotypes. *ABCB1* triple TT diplotype was not also associated with the plasma concentration of naldemedine ($P = 0.924$).

3.4 | Associations with plasma 4β-OHC

The median and IQR of the plasma 4β-OHC level were 33 and 26–50 ng/mL, respectively. The plasma 4β-OHC level and serum total cholesterol normalized plasma 4β-OHC level (4β-OHC/TC) were lower in patients with *CYP3A5*3/*3* than in those with **1* allele ($P < 0.001$ in both cases) (Figure 2). The plasma concentration of naldemedine was negatively correlated with the plasma 4β-OHC level ($r_s = -0.322$, $P = 0.025$) and 4β-OHC/TC ($r_s = -0.294$, $P = 0.043$). Gender was not associated with plasma 4β-OHC or naldemedine ($P = 0.309$ and $P = 0.425$, respectively).

3.5 | Relationship with cancer cachexia

The serum levels of IL-6 and CRP were higher in patients with refractory cachexia than in those with precachexia and cachexia ($P = 0.011$ and $P = 0.001$, respectively, Table S2). Although a statistically significant difference was not observed, the serum AGP level was also higher in refractory cachexia ($P = 0.057$). The patients with GPS 2 had higher levels of serum IL-6 ($P < 0.001$), CRP ($P < 0.001$), and AGP ($P = 0.010$) than those with GPS 0–1. The plasma naldemedine concentration was lower in patients with refractory cachexia than in those with precachexia and cachexia ($P = 0.047$) (Figure 3). GPS was not statistically associated with the plasma naldemedine concentration. The plasma naldemedine concentration was not directly associated with the serum levels of IL-6 ($r_s = -0.156$, $P = 0.289$), CRP ($r_s = -0.029$, $P = 0.843$), and AGP ($r_s = 0.116$, $P = 0.433$).

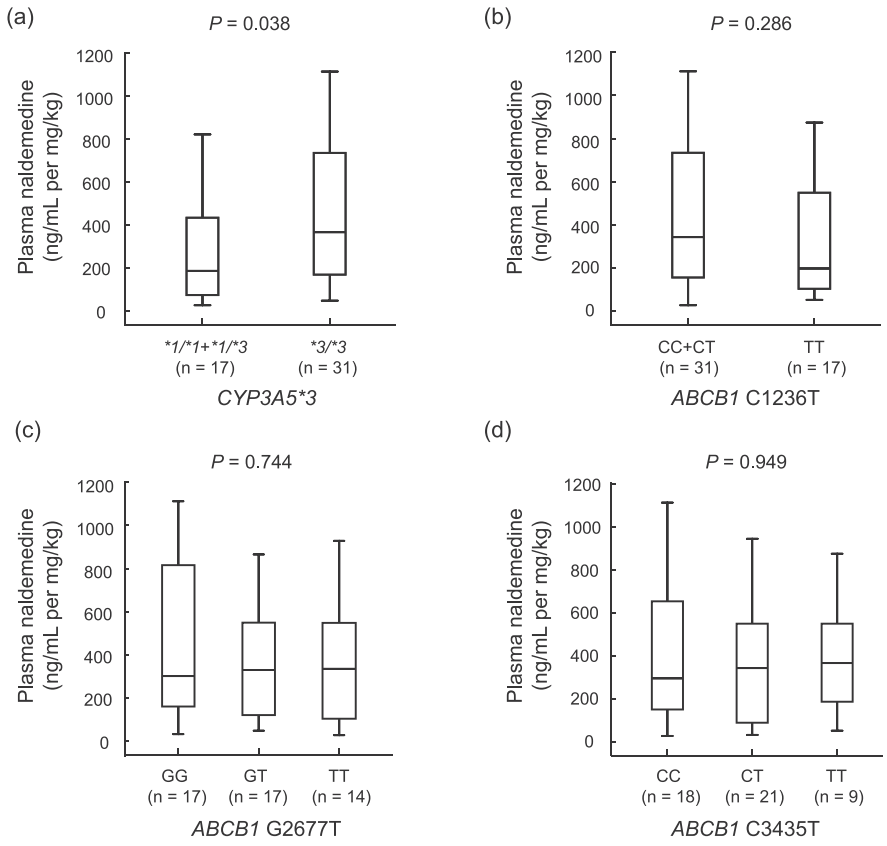

FIGURE 1 Plasma naldemedine between each genotype of CYP3A5 and ABCB1. The horizontal line indicates genotype of *CYP3A5*3* (a), *ABCB1* C1236T (b), *ABCB1* G2677T (c), and *ABCB1* C3435T (d). Box plots represent the median, 25th, and 75th percentiles. The whiskers indicate the range and extend within 1.5 times the length of the inner quartiles. The Mann–Whitney *U* test was used in (a) and (b), and the Kruskal–Wallis test was used in (c) and (d).

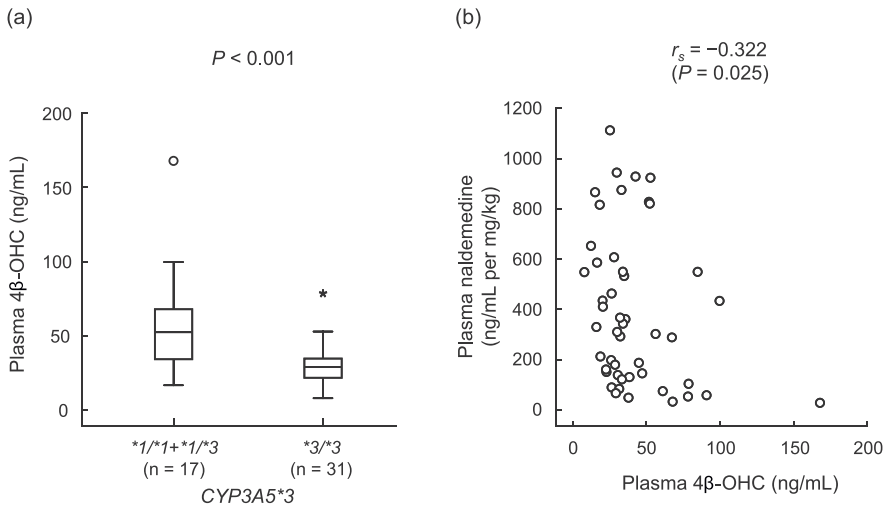

FIGURE 2 Association of plasma 4β-hydroxycholesterol (4β-OHC) with CYP3A5 genotype (a) and plasma naldemedine (b). Difference in plasma 4β-OHC between *CYP3A5*3* genotypes was analyzed using the Mann–Whitney *U* test. The correlations between 4β-OHC and plasma naldemedine were evaluated using Spearman's rank correlation coefficient test.

3.6 | Factors related to bowel movements and adverse effects

Analysis of SBM responder was conducted in 36 patients. Absolute plasma naldemedine was higher in the SBM responder group than in the non-responder group ($P = 0.047$, Figure S1). The area under the receiver operating characteristic curve of absolute plasma naldemedine for SBM was 0.694 (95% confidence interval: 0.522–0.866, $P = 0.046$). The cut-off value of absolute plasma naldemedine was 1.26 ng/mL in the curve and its sensitivity and specificity were 61% and 72%, respectively. A high absolute concentration of plasma naldemedine and the presence of *CYP3A5*3/*3* increased the number of SBM responders in univariate analysis (Table 2). Being an SBM responder was not related to OPRM1 and COMT genotypes. Starting naldemedine administration within 2 days after opioid treatment increased the number of SBM responders. GPS 2 and concomitant antacids were not associated with the number of SBM responders in the univariate regressions. Figure S2

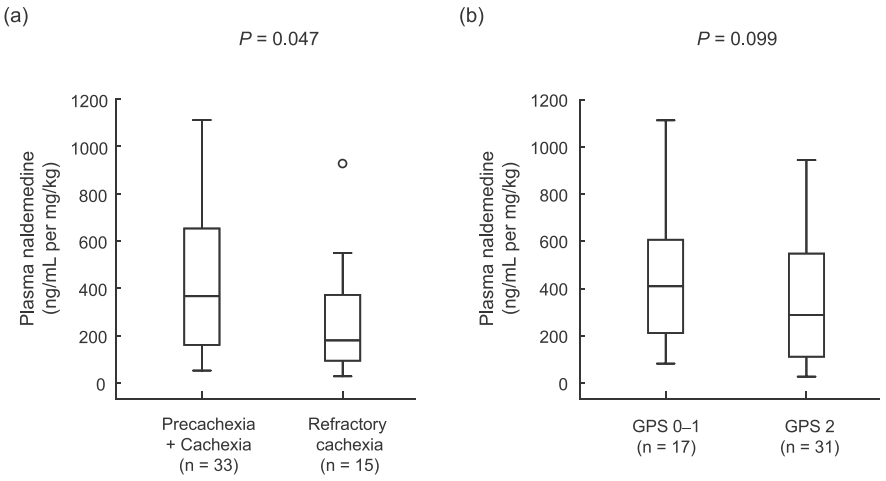

FIGURE 3 Plasma naldemedine between cachexia status (a) and Glasgow prognostic score (GPS) (b). Box plots represent the median, 25th, and 75th percentiles. The whiskers indicate the range and extend within 1.5 times the length of the inner quartiles. The Mann–Whitney *U* test was used.

TABLE 2 Univariate and multivariate analyses of spontaneous bowel movement (SBM) responders.

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
Plasma absolute naldemedine, ng/mL	2.30	1.02–5.20	0.045	3.58	1.13–11.4	0.030
CYP3A5, **3/*3*	4.38	1.03–18.6	0.046			
OPRM1, 118AG + 118GG	0.509	0.135–1.92	0.319	0.586	0.091–3.79	0.574
COMT, 158Val/Met + 158Met/Met	0.308	0.077–1.23	0.096	0.153	0.019–1.22	0.076
Starting naldemedine within 2 days of opioid initiation	12.3	2.55–59.0	0.002	17.3	2.27–131	0.006
Co-administration of other laxatives	0.127	0.027–0.606	0.010			
GPS 2	2.08	0.519–8.34	0.301			
Concomitant antacids	0.564	0.285–1.12	0.100			

Note: Binary logistic regression (forced entry method) was used in multivariate analysis. The following factors (*CYP3A5*3/*3*, co-administration of other laxatives, GPS 2, and concomitant antacids) were excluded from the multivariate analysis because these factors were related to plasma naldemedine concentration.
Abbreviations: CI, confidence interval; COMT, catechol-*O*-methyltransferase; CYP, cytochrome P450; GPS, Glasgow prognostic score; OPRM1, μ1-opioid receptor; OR, odds ratio.

showed that the median plasma naldemedine was similar in patients who took antacids with GPS 0–1 and those who did not take antacids with GPS 2, but that SBM responder rate tended to decrease in patients with antacids. The associations of bowel movements with opioid and cancer types were described in Table S3. After adjustment for covariate, plasma naldemedine and starting naldemedine within 2 days of opioid initiation increased the number of SBM responders. None of the above factors was related to SBM of ≥4 times per week (Tables S4, S5). Diarrhea (≥grade 1) or loose stool (Bristol scale ≥ 6) was observed in 14.6% patients. No difference was observed in the absolute concentration of plasma naldemedine between patients with or without diarrhea. Opioid withdrawal syndrome was not observed in this study.

4 | DISCUSSION

Naldemedine efficacy and adverse effects varied in advanced cancer patients. This study investigated the impacts of genetic polymorphisms and cancer cachexia on plasma naldemedine and its clinical responses. Plasma naldemedine was higher in patients with CYP3A5 impairment, while it decreased with the progression of cachexia. The plasma concentration of naldemedine and the timing of starting its administration were associated with bowel movements under OIC. These findings suggest that plasma naldemedine, related to CYP3A5 genotype, in addition to the timing of naldemedine initiation, need to be considered in OIC management using naldemedine. To the best of our knowledge, this is the first report that has characterized naldemedine pharmacokinetics and efficacy from the aspects of CYP3A5 genotype and cachexia status.

Plasma naldemedine differed approximately fourfold between individuals according to the IQR value. The enrolled patients had a median plasma naldemedine concentration of 1.1 ng/mL at 24 h after dosing. A population pharmacokinetic model including healthy subjects of several races showed a mean plasma naldemedine concentration of approximately 0.5 ng/mL at 24 h after dosing [27]. In the present study, seven

patients treated with concomitant aprepitant, a mild-to-moderate CYP3A4 inhibitor [28], had a higher plasma naldemedine. The enrolled cancer patients may have cancer-derived nutritional disorders and inflammation due to their serum total protein and CRP levels. Our data suggest that the study population has some factors that cause the fluctuation of plasma naldemedine in patients with cancer.

Plasma naldemedine was approximately twofold higher in patients with the homozygous *CYP3A5*3* allele than in those with the homozygous or heterozygous **1* allele. The **3*/**3* allele is associated with complete loss of CYP3A5 activity, and the patients with *CYP3A5*3*/**3* had a twofold higher concentration of CYP3A5 substrates [29, 30]. These data indicate the predominant contribution of CYP3A5 to naldemedine metabolism in cancer patients. Since the allele frequency of *CYP3A5*3* in the Japanese population is approximately 0.7 [31], the genotype is potentially responsible for the large variation in plasma naldemedine in our study. Lower CYP3A activity in patients with homozygous *CYP3A5*3* was confirmed by plasma 4β-OHC. These data support the possibility that the CYP3A5 genotype is one of the factors determining an individual concentration of plasma naldemedine.

ABCB1 genetic polymorphisms were not factors related to interindividual variation of plasma naldemedine in this study population. Several studies have reported that each ABCB1 genotype and its 1236TT-2677TT-3435TT diplotype were associated with high concentrations of P-gp substrates [32–34]. Increased naldemedine exposure with a concomitant P-gp inhibitor was considered to be due to decreased intestinal absorption [12]. With regard to absorption, it has been reported that absorption of weak basic drug is reduced due to decreased solubility [35]. Given that naldemedine has acid dissociation constants of 5.4 and 9.5, a lower plasma naldemedine in patients with concomitant antacids may be caused by poor solubility in the intestine. In our study population, factors such as concomitant antacids and magnesium oxide might be considered to override the genetic impacts on absorption. Our data suggest that the impacts of ABCB1 genotypes on OIC management are negligible from the viewpoint of naldemedine exposure.

Plasma naldemedine decreased with the progression of cachexia in this study. Chronic inflammation in cachexia has been shown to cause the downregulation of CYP3A4 and P-gp expression [36, 37]. High serum IL-6 and acute-phase proteins in the enrolled patients indicated a highly inflammatory condition. These data contradicted our hypothesis that plasma naldemedine increases with the progression of cachexia due to reduced CYP3A4 and P-gp activity. Serum IL-6 in the enrolled patients (median, 36 pg/mL) was less involved in the reduction of CYP3A5 activity on the basis of the half-maximal inhibitory concentration of CYP3A5 [38]. Since neither serum albumin nor AGP was associated with plasma naldemedine, the variation in protein binding that contributed to excretion was considered to be irrelevant to plasma naldemedine. Advanced cancer patients had a lower concentration of plasma ghrelin, a hormone related to gastric acid secretion [39]. Cachectic patients with decreased ghrelin might have a low intestinal absorption due to weakened intestinal acidity.

A high plasma naldemedine concentration was responsible for the improvements of bowel movement in this study. An earlier study reported the dose-dependent efficacy of naldemedine on bowel movements [22]. *CYP3A5*3*/**3*, related to plasma naldemedine, was also involved in the high frequency of SBM responders. *OPRM1* c.118A > G and *COMT* p.Val158Met decreased the affinity and expression of OPRM1 [40, 41]. In the present study, these variants might have had little effect on naldemedine binding to OPRM1 and did not affect the naldemedine efficacy. Earlier naldemedine administration after starting opioid analgesics is needed to obtain an improvement in defecation, which is consistent with earlier reports [42]. Lower SBM responders among patients with concomitant laxatives reflected lower plasma naldemedine caused by magnesium oxide. According to the results in Figure S2, concomitant antacids may have greater effect on plasma naldemedine and bowel movements than decreased ghrelin secretion in cachexia. Risk factors for adverse effects were not identified in this study. Our data support the idea that naldemedine appears to be relatively safe to use in patients with advanced cancer.

This study has several limitations. First, most of the enrolled patients were in advanced cachexia. More than 70% of the patients had a GPS of 2, and albumin and CRP in patients with a GPS of 1 were mostly near the borderline values. GPS was not appropriate to detect cachexia in this study. A comparison with healthy volunteers would reveal the impact of cachexia on naldemedine pharmacokinetics. Second, a sample size of this study was small and a statistical power in Mann–Whitney *U* test was low. Since there were underlying risks of missing statistically significant differences in the present study, further study with a larger sample size might reveal the impact of ABCB1 genotypes on plasma naldemedine. Third, confounding factors related to defecation were not fully excluded. The enrolled patients had various types of cancer, and approximately half of the patients received individualized cancer chemotherapies. Cancer types, chemotherapy, and opioid types commonly influence constipation rate. Stratified analysis with a large number of patients would provide more information about the relation between plasma naldemedine and bowel movements for each cancer type or concomitant drug. Fourth, blood sampling was conducted at only one point at 24 h after

dosing. Although the area under the curve is an ideal marker of plasma exposure to drugs, one point in the elimination phase is used as a minimally invasive surrogate marker of drug clearance. Further studies, including systemic drug exposure analyses, may lead to a better understanding of the interindividual variations in clinical responses to naldemedine.

Our observation study suggests that naldemedine can be used safely in cachectic cancer patients. In contrast, cachexia staging for naldemedine-treated cancer patients might reveal a lower naldemedine exposure. To date, naldemedine dosing is commonly fixed without dose-adjustment in cancer patients. SBM is expected to be obtained at a pre-dose plasma naldemedine concentration of > 1.3 ng/mL. The homozygous *CYP3A5*3* patients had a higher naldemedine exposure. CYP3A5 genotyping potentially leads to a better clinical response to naldemedine in **1* allele carriers by increasing its dose. In addition, concomitant use of aprepitant or antacids is potentially involved in the excessive or poor response to naldemedine. Concomitant use of magnesium oxide has a potential risk of poor clinical response, although it is usually used with naldemedine as a laxative. Further intervention studies is needed to verify the clinical implications of cachectic staging and CYP3A5 genotyping for OIC management using naldemedine in cancer patients.

5 | CONCLUSION

Plasma naldemedine increased under decreased activity of CYP3A5 in cancer patients. Cachectic patients with a higher serum IL-6 level had a lower plasma naldemedine concentration. Plasma naldemedine, related to CYP3A5 genotype, and the initiation timing of naldemedine were associated with bowel movements.

AUTHOR CONTRIBUTIONS

Emi Nakatsugawa and Takafumi Naito designed the protocol with input from Junichi Kawakami. Emi Nakatsugawa and Kaito Shibata recruited patients and performed blood sampling with assistance from Ryo Kitajima. Emi Nakatsugawa and Kaito Shibata collected drug and biomarker level results and analyzed and interpreted data with assistance of Takafumi Naito. Emi Nakatsugawa wrote the first draft of the manuscript. All authors reviewed the manuscript and approved the final version of the manuscript.

ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Number 21H04204, 21K06664, and 22H04287.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ORCID

Takafumi Naito https://orcid.org/0000-0002-7447-3789

REFERENCES

1. Uritsky TJ. Methylnaltrexone: peripherally acting μ-opioid receptor antagonist. *J Adv Pract Oncol*. 2019;10(1):62-67.
2. Kalso E, Edwards JE, Moore AR, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380. doi:10.1016/j.pain.2004.09.019
3. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*. 2014;370(25):2387-2396. doi:10.1056/NEJMoa1310246
4. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European patient survey (PROBE 1). *Pain Med*. 2009;10(1):35-42. doi:10.1111/j.1526-4637.2008.00495.x
5. Katakami N, Oda K, Tauchi K, et al. Phase IIb, randomized double-blind, placebo-controlled study of naldemedine for the treatment of opioid-induced constipation in patients with cancer. *J Clin Oncol*. 2017;35(17):1921-1928. doi:10.1200/JCO.2016.70.8453
6. Product information for Symproic. The Japan Pharmaceuticals and Medical Devices Agency https://www.pmda.go.jp/ (last accessed on 9 April 2023).
7. Prescribing information for SYMPROIC (Reference ID: 4074014). The US Food and Drug Administration https://www.accessdata.fda.gov/ (last accessed on 9 April 2023).
8. Rizmoic: EPAR—product information. The European Medicines Agency https://www.ema.europa.eu/ (last accessed on 9 April 2023).
9. Björkhem-Bergman L, Bäckström T, Nylén H, et al. Comparison of endogenous 4β-hydroxycholesterol with midazolam as markers for CYP3A4 induction by rifampicin. *Drug Metab Dispos*. 2013;41(8):1488-1493. doi:10.1124/dmd.113.052316
10. Diczfalusy U, Nylén H, Elander P, Bertilsson L. 4β-Hydroxycholesterol, an endogenous marker of CYP3A4/5 activity in humans. *Br J Clin Pharmacol*. 2011;71(2):183-189. doi:10.1111/j.1365-2125.2010.03773.x
11. Ishida T, Naito T, Sato H, Kawakami J. Relationship between the plasma fentanyl and serum 4β-hydroxycholesterol based on CYP3A5 genotype and gender in patients with cancer pain. *Drug Metab Pharmacokinet*. 2016;31(3):242-248. doi:10.1016/j.dmpk.2016.04.001
12. Fukumura K, Kawaguchi N, Ishibashi T, Kubota R, Tada Y, Ogura E. Clinical drug-drug interaction studies to evaluate the effects of a P-glycoprotein inhibitor, CYP3A inhibitors, and a CYP3A inducer on the pharmacokinetics of naldemedine in healthy subjects. *Clin Drug Investig*. 2020;40(6):529-540. doi:10.1007/s40261-020-00902-w
13. Sun H, Dai H, Shaik N, Elmquist WF. Drug efflux transporters in the CNS. *Adv Drug Deliv Rev*. 2003;55(1):83-105. doi:10.1016/s0169-409x(02)00172-2
14. Kim KA, Park PW, Park JY. Effect of ABCB1 (MDR1) haplotypes derived from G2677T/C3435T on the pharmacokinetics of amlodipine in healthy subjects. *Br J Clin Pharmacol*. 2007;63(1):53-58. doi:10.1111/j.1365-2125.2006.02733.x
15. Turiján-Espinoza E, Ruíz-Rodríguez VM, Uresti-Rivera EE, et al. Clinical utility of ABCB1 and ABCG2 genotyping for assessing the clinical and pathological response to FAC therapy in Mexican breast cancer patients. *Cancer Chemother Pharmacol*. 2021;87(6):843-853.
16. Yu Z, Wen L, Shen X, Zhang H. Effects of the OPRM1 A118G polymorphism (rs1799971) on opioid analgesia in cancer pain: a

systematic review and meta-analysis. *Clin J Pain*. 2019;35(1):77-86.
17. Hooten WM, Biernacka JM, O'Brien TG, Cunningham JM, Black JL. Associations of catechol-O-methyltransferase (rs4680) single nucleotide polymorphisms with opioid use and dose among adults with chronic pain. *Pain*. 2019;160(1):263-268.
18. Trobec K, Kos MK, von Haehling S, et al. Pharmacokinetics of drugs in cachectic patients: a systematic review. *PLoS ONE*. 2013;8(11):e79603.
19. McNamara MJ, Alexander HR, Norton JA. Cytokines and their role in the pathophysiology of cancer cachexia. *JPEN J Parenter Enteral Nutr*. 1992;16(6 Suppl):50S-55S.
20. Tanaka H, Naito T, Sato H, Hiraide T, Yamada Y, Kawakami J. Impact of CYP genotype and inflammatory markers on the plasma concentrations of tramadol and its demethylated metabolites and drug tolerability in cancer patient. *Eur J Clin Pharmacol*. 2018;74(11):1461-1469.
21. Takeshita Y, Fujikawa S, Serizawa K, et al. New BBB model reveals that IL-6 blockade suppressed the BBB disorder, preventing onset of NMOSD. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(6):e1076.
22. Fukumura K, Yokota T, Baba Y, Arjona Ferreira JC. Phase 1, randomized, double-blind, placebo-controlled studies on the safety, tolerability, and pharmacokinetics of naldemedine in healthy volunteers. *Clin Pharmacol Drug Dev*. 2018;7(5):474-483.
23. Drug development and drug interactions. Table of substrates, inhibitors and inducers. The US Food and Drug Administration https://www.fda.gov/ (last accessed on 21 January 2023).
24. Joshi P, Vishwakarma RA, Bharate SB. Natural alkaloids as P-gp inhibitors for multidrug resistance reversal in cancer. *Eur J Med Chem*. 2017;138:273-292.
25. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-495.
26. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer*. 2003;89(6):1028-1030.
27. Kubota R, Fukumura K, Wajima T. Population pharmacokinetics and exposure-response relationships of naldemedine. *Pharm Res*. 2018;35(11):225.
28. Hsyu PH, Pignataro DS, Matschke K. Effect of aprepitant, a moderate CYP3A4 inhibitor, on bosutinib exposure in healthy subjects. *Eur J Clin Pharmacol*. 2017;73(1):49-56.
29. Takashina Y, Naito T, Mino Y, Yagi T, Ohnishi K, Kawakami J. Impact of CYP3A5 and ABCB1 gene polymorphisms on fentanyl pharmacokinetics and clinical responses in cancer patients undergoing conversion to a transdermal system. *Drug Metab Pharmacokinet*. 2012;27(4):414-421.
30. Hirano K, Naito T, Mino Y, Takayama T, Ozono S, Kawakami J. Impact of CYP3A5 genetic polymorphism on cross-reactivity in tacrolimus chemiluminescent immunoassay in kidney transplant recipients. *Clin Chim Acta*. 2012;414:120-124.
31. Fukuen S, Fukuda T, Maune H, et al. Novel detection assay by PCR-RFLP and frequency of the CYP3A5 SNPs, CYP3A5*3 and *6, in a Japanese population. *Pharmacogenetics*. 2002;12(4):331-334.
32. Naito T, Mino Y, Aoki Y, et al. ABCB1 genetic variant and its associated tacrolimus pharmacokinetics affect renal function in patients with rheumatoid arthritis. *Clin Chim Acta*. 2015;445:79-84.
33. Hawwa AF, McKiernan PJ, Shields M, Millership JS, Collier PS, McElnay JC. Influence of ABCB1 polymorphisms and haplotypes on tacrolimus nephrotoxicity and dosage requirements in children with liver transplant. *Br J Clin Pharmacol*. 2009;68(3):413-421.
34. Salama NN, Yang Z, Bui T, Ho RJ. MDR1 haplotypes significantly minimize intracellular uptake and transcellular P-gp substrate transport in recombinant LLC-PK1 cells. *J Pharm Sci*. 2006;95(10):2293-2308.
35. Gesenberg C, Mathias NR, Xu Y, et al. Utilization of in vitro, in vivo and in silico tools to evaluate the pH-dependent absorption of a BCS class II compound and identify a pH-effect mitigating strategy. *Pharm Res*. 2019;36(12):164.
36. Morgan ET, Goralski KB, Piquette-Miller M, et al. Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. *Drug Metab Dispos*. 2008;36(2):205-216.
37. Saib S, Delavenne X. Inflammation induces changes in the functional expression of P-gp, BCRP, and MRP2: an overview of different models and consequences for drug disposition. *Pharmaceutics*. 2021;13(10):1544.
38. Dickmann LJ, Patel SK, Rock DA, Wienkers LC, Slatter JG. Effects of interleukin-6 (IL-6) and an anti-IL-6 monoclonal antibody on drug-metabolizing enzymes in human hepatocyte culture. *Drug Metab Dispos*. 2011;39(8):1415-1422.
39. Legakis I, Stathopoulos J, Matzouridis T, Stathopoulos G. Decreased plasma ghrelin levels in patients with advanced cancer and weight loss in comparison to healthy individuals. *Anticancer Res*. 2009;29(10):3949-3952.
40. Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. *Anesthesiology*. 2014;121(4):825-834.
41. Mitchell JM, O'Neil JP, Jagust WJ, Fields HL. Catechol-O-methyltransferase genotype modulates opioid release in decision circuitry. *Clin Transl Sci*. 2013;6(5):400-403.
42. Kanbayashi Y, Shimizu M, Ishizuka Y, Sawa S, Yabe K, Uchida M. Factors associated with non-response to naldemedine for opioid-induced constipation in cancer patients: a subgroup analysis. *PLoS ONE*. 2022;17(12):e0278823.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nakatsugawa E, Naito T, Shibata K, Kitajima R, Kawakami J. Impacts of genetic polymorphisms and cancer cachexia on naldemedine pharmacokinetics and bowel movements in patients receiving opioid analgesics. *Fundam Clin Pharmacol*. 2024;1-10. doi:10.1111/fcp.12976