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Contributions of authors

Nozomi Yoshikawa performed the research. Takafumi Naito, Tatsuya Yagi, and Junichi Kawakami were involved in developing the study concept and design. All authors analyzed the data, contributed to the writing of the manuscript and approved the final manuscript for submission.

Ethics

The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments. This study protocol (#EG14-356) was approved by the Ethics Committee of Hamamatsu University School of Medicine. All patients were provided with information about the scientific aim of this study and gave written informed consent before participation.

Abstract

BACKGROUND: Cancer patients receiving pregabalin potentially have a high incidence of central nervous system (CNS) symptoms. The purpose of this study was to explore clinical factors influencing the incidence of CNS symptoms, including plasma pregabalin exposure, cancer cachexia, and opioid analgesic co-treatment.

METHODS: Sixty-eight cancer patients receiving twice-daily pregabalin were enrolled. Plasma concentrations of pregabalin, clinical laboratory data, opioid analgesic co-treatment, and the Glasgow Prognostic Score (GPS), which is an inflammation-based cachexia score, were considered as clinical factors. The incidence of CNS symptoms was collected from the patients' medical records. The pre-dose plasma concentrations of pregabalin at steady-state was determined by ultra-high-performance liquid chromatography.

RESULTS: The steady-state trough plasma pregabalin concentrations showed a large variability with an interquartile range of 0.43-1.2 mg/L per mg/kg and was negatively correlated with estimated glomerular filtration rate (eGFR). C-reactive protein (standardized partial regression coefficient, $\beta = 0.31$) and opioid analgesic co-treatment ($\beta = 0.24$) were also identified in addition to eGFR ($\beta = -0.60$) in the multiple regression analysis. The incidence of CNS symptoms was significantly increased with opioid analgesic co-treatment and a higher GPS but not with the absolute value of plasma pregabalin concentrations, eGFR, nor other clinical laboratory data.

CONCLUSIONS: In cancer patients, steady-state trough plasma pregabalin concentrations were altered with renal function, systemic inflammation, and opioid analgesic co-treatment. However, a higher incidence of CNS symptoms observed in cancer patients on pregabalin was more related to cachexia and opioid analgesic co-treatment than to altered pregabalin concentrations.

KEYWORDS: pregabalin; central nervous system (CNS) symptoms; plasma concentrations; cancer cachexia; opioid analgesics

Introduction

Pregabalin binds to the α2δ subunit of voltage-gated calcium channels, thus reducing the release of neurotransmitters including substance P and glutamic acid at presynaptic terminals, which thereby results in analgesic activity for neuropathic pain.[1] Pregabalin is largely absorbed from the intestine, neither metabolized nor bound to plasma protein and is predominantly excreted in the urine in the unchanged form.[2] Patients on pregabalin experience central nervous system (CNS) symptoms such as dizziness and somnolence.[3] These symptoms are often observed during the early period of pregabalin treatment and could potentially trigger the discontinuation of the treatment.[3,4] Since the elimination of pregabalin in plasma is associated with the glomerular filtration rate, the pregabalin dose is commonly adjusted according to renal function.[5] However, dose-adjustment based on renal function does not markedly reduce the incidence of adverse effects in patients treated with pregabalin.[6]

Combination therapy of pregabalin and opioid analgesics often enables the reduction of opioid consumption[7,8] and provides better pain relief than analgesic monotherapy in patients with cancer pain.[9,10] However, cancer patients receiving pregabalin and opioid analgesics have a high incidence of CNS symptoms and poor tolerability.[11] To date, besides opioids, the factors that increase the incidence of adverse effects of pregabalin have not been fully characterized in clinical settings. Although the dose-response relationship of pregabalin has been confirmed in patients with neuropathic pain,[12] it has not been in cancer patients combined with opioids. In addition, the relationship between plasma pregabalin and CNS symptoms is unclear in any indications.

Most of the patients receiving the pregabalin-opioid combination therapy for the treatment of

intractable pain suffer from advanced cancer. These patients show elevated levels of serum proinflammatory cytokines such as interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α).[13] Those cytokines lead to cachexia, symptoms including sarcopenia, depression, somnolence and delirium.[14] Since cancer cachexia is accompanied by declines in hepatic metabolism and the renal elimination of drugs,[15,16] cachectic cancer patients could potentially suffer from adverse effects caused by delayed drug elimination. Our previous reports also demonstrated that cachectic cancer patients had delayed oxycodone elimination and a higher incidence of somnolence.[17,18] There is no clinical data suggesting that cancer cachexia influences plasma pregabalin levels or the incidence of CNS symptoms.

There has been a growing interest in the importance of cachexia management for cancer patients in recent years.[19] However, the influence of cachexia and opioid analgesic co-treatment on pregabalin pharmacokinetics and clinical response to pregabalin has not been fully clarified. The purpose of this study was to explore clinical factors influencing the plasma concentration of pregabalin and the incidence of CNS symptoms in cancer patients.

Materials and Methods

PATIENTS AND BLOOD SAMPLING

The present study is an observational study conducted at Hamamatsu University Hospital (Hamamatsu, Japan). A total of 80 Japanese cancer patients treated with oral pregabalin capsules (Lyrica, Pfizer Japan, Tokyo) twice-daily for cancer pain were recruited, and 68 patients were eventually enrolled. Twelve patients were excluded according to the following exclusion criteria: (1) patients who were not receiving an equal dose of pregabalin as a twice-daily administration; (2) patients who were being co-treated or treated within 1 week with anticancer drugs; (3) patients who were being co-treated with an organic cation transporter inhibitor such as quinidine, verapamil, or cimetidine; (4) patients who were being co-treated

with a strong drug-metabolizing enzyme inducer or inhibitor such as carbamazepine, phenobarbital, phenytoin, rifampicin, a triazole antifungal agent, or a macrolide antibiotic; (5) patients who were being co-treated with a long-acting benzodiazepines; (6) patients with kidney dysfunction (serum creatinine > 2.0 mg/dL) or liver dysfunction (serum total bilirubin > 2.0 mg/dL); (7) patients with a cerebrovascular disease or brain metastasis; and (8) patients with poor medication adherence based on an interview by a pharmacist. All patients received a fixed dose of pregabalin for at least 1 week at the time of blood sampling. Blood specimens were drawn into tubes at 12 hours after the evening dosing in order to determine the steady-state trough plasma pregabalin concentration. This study was registered in the University Hospital Medical Information Network (UMIN000024658).

DETERMINATION OF PLASMA PREGABALIN CONCENTRATIONS

After plasma protein precipitation, pregabalin and gabapentin as an internal standard were derivatized by 4-fluoro-7-nitrobenzofurazan. The plasma concentration of pregabalin was determined by an isocratic ultra-high performance liquid chromatography system coupled to a fluorescence detector as described in our previous report.[20] The calibration curve of the plasma pregabalin concentrations was linear over the range of 0.05-10 mg/L (r > 0.999). The intra-day accuracy and imprecision of the method were 98.3-99.8% and within 4.3%, respectively, while the inter-day accuracy and imprecision were 103.2-107.1% and within 4.1%, respectively. The lower limit of quantification of plasma pregabalin was 0.05 mg/L. The steady-state trough plasma pregabalin concentrations were adjusted by dose and body weight and were used to evaluate the interindividual variation in pregabalin pharmacokinetics. The absolute value of plasma pregabalin concentrations was used to assess the relationship with the incidence of CNS symptoms.

EVALUATION OF RENAL FUNCTION

The estimated glomerular filtration rate (eGFR) was calculated as a renal function marker based on serum creatinine using the following equation developed for Japanese[21]: eGFR (mL/min/1.73 m^2) = 194 × (Serum creatinine, mg/dL)$^{-1.094}$ × (Age, years)$^{-0.287}$ × 0.739 (if female) × (Body surface area, m^2) / 1.73. Serum creatinine was measured using an automated enzymatic assay. Body surface area (m^2) was estimated using the following equation[22]: 0.007184 × (Weight, kg)$^{0.425}$ × (Height, cm)$^{0.725}$.

CANCER CACHEXIA SCORE

The Glasgow Prognostic Score (GPS), which is based on the serum levels of albumin and C-reactive protein (CRP),[23] was used to obtain a cancer cachexia score. Patients with hypoalbuminemia (< 3.5 g/dL) and an elevated serum CRP (> 1.0 mg/dL) were classified into the group of GPS 2. Patients who corresponded to only one or none of the above criteria were classified into the groups of GPS 1 or 0, respectively. Serum albumin levels were measured by the bromocresol purple method. Serum CRP levels were determined by latex agglutination turbidimetric immunoassay.

EVALUATION OF CNS SYMPTOMS

The incidences of CNS symptoms including somnolence and dizziness were collected from the patients' medical records by an experienced member of our research staff. The period for evaluating the presence or absence of CNS symptoms was within 1 week before and after the blood sampling. For enrolled patients treated with a fixed dose of pregabalin for at least 1 week at the blood sampling, the incidence of CNS symptoms for a week before and after the blood sampling were investigated. The severity of the CNS symptoms was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A grade ≥ 1 of CTCAE was regarded as a positive adverse effect. Information on the concomitant use of opioid analgesics, which has the potential to modify CNS symptoms, was collected from

medical records. Opioid analgesics in this study included oxycodone, fentanyl, morphine, codeine, methadone, tramadol, and tapentadol.

STATISTICAL ANALYSIS

All data were analyzed using SPSS statistics version 22 (IBM Japan, Tokyo, Japan). The relationships between the steady-state trough plasma pregabalin concentrations and eGFR, age, the serum level of albumin, or serum CRP were assessed in simple regression analysis. The influences of concomitant use of opioid analgesics, gender, or GPS on the steady-state trough plasma pregabalin concentrations were examined using the Mann-Whitney *U* test or Kruskal-Wallis test. Multiple regression analysis with the standardized partial regression coefficient (β) was used to evaluate the association between the steady-state trough plasma pregabalin concentrations and the above clinical factors. The correlations between the absolute value of plasma concentration and a dose of pregabalin were evaluated using Pearson's test. The absolute value of plasma pregabalin concentrations in patients with and without the CNS symptoms was compared using the Mann-Whitney *U* test. The odds ratio (OR) with a 95% confidence interval (CI) for the incidence of CNS symptoms were calculated using univariate and multivariate logistic regression analysis regarding the above clinical factors, body weight or body mass index. Serum levels of albumin, CRP, body weight, or body mass index were not analyzed simultaneously with GPS in multiple regression and multivariate logistic regression analysis in order to avoid multicollinearity. A *p*-value of 0.05 or less was considered statistically significant.

Results

PATIENTS

Table 1 summarizes the characteristics of the patients included in this study. The patients suffered from urinary system cancer (n = 20), gastrointestinal cancer (n = 15), head and neck

cancer (n = 11), lung cancer (n = 9), hematologic malignancy (n = 9), or other types of cancer (n = 4). All patients received 25-200 mg twice-daily pregabalin, and 17 of them were co-treated with the following opioid analgesics: oral oxycodone (n = 11), transdermal fentanyl (n = 5), and oral morphine (n = 1).

INTERINDIVIDUAL VARIATION IN PLASMA PREGABALIN CONCNETRATIONS

The median and interquartile range (IQR) of the absolute value of plasma pregabalin concentrations were 1.9 and 1.1-2.9 mg/L, respectively. The absolute value of plasma pregabalin concentrations was significantly correlated with the pregabalin dose (mg/kg) (r = 0.32, $p < 0.01$). The median of the steady-state trough plasma pregabalin concentrations was 0.70 (IQR, 0.43-1.1) mg/L per mg/kg. A large variation in the steady-state trough plasma pregabalin concentration was observed in these cancer patients.

CLINICAL FACTORS RELATED TO THE PLASMA PREGABALIN

The steady-state trough plasma pregabalin concentrations were negatively correlated with the eGFR (R^2 = 0.25, $p < 0.01$), but not with the serum level of CRP (R^2 = 0.05, p = 0.08) as assessed using simple regression analysis (Figure 1). Although the median of steady-state trough plasma pregabalin concentrations in patients co-treated with opioid analgesics tended to be higher than those in patients without opioid analgesics (1.1 and 0.66 mg/L per mg/kg, respectively), the difference did not reach statistical significance (p = 0.27). Multiple linear regression analysis identified eGFR (β = -0.60, $p < 0.01$), the serum level of CRP (β = 0.31, $p < 0.01$), and concomitant use of opioid analgesics (β = 0.24, p = 0.02) as independent variables significantly related to the steady-state trough plasma pregabalin concentrations, while age, the serum level of albumin, gender, or GPS were not identified (Table 2).

RELATIONSHIPS BETWEEN THE FACTORS ASSOCIATED WITH PLASMA PREGABALIN CONCENTRATIONS

The serum levels of CRP in patients co-treated with opioid analgesics were significantly higher than in those not co-treated ($p = 0.03$). The eGFR was not significantly correlated with serum CRP ($R^2 = 0.05$, $p = 0.08$). No difference in the mean eGFR values was observed between patients with and without opioid analgesics co-treatment ($p = 0.09$).

CLINICAL FACTORS ASSOCIATED WITH THE INCIDENCE OF CNS SYMPTOMS

Twenty-five out of 68 patients had CNS symptoms in this study population. CNS symptoms observed were grade I somnolence (n = 17) and grade I dizziness (n = 8). There were 4, 9, and 12 patients with CNS symptoms in the GPS 0, 1, and 2 groups, respectively. As suggested by univariate logistic regression analysis, the incidence of CNS symptoms was significantly associated with the serum levels of albumin (OR 0.49, 95% CI 0.25-0.95, $p = 0.04$), concomitant use of opioid analgesics (OR 7.0, 95% CI 2.1-24, $p < 0.01$), and GPS (OR 2.2, 95% CI 1.2-4.2, $p = 0.01$), but not with the absolute value of plasma pregabalin concentrations, eGFR, age, serum CRP concentrations, or gender (Table 3). Multivariate logistic regression analysis suggested the significant influence of concomitant use of opioid analgesics (OR 7.0, 95% CI 2.1-24, $p < 0.01$) on the incidence of CNS symptoms. Among 17 patients treated with pregabalin and opioid analgesics concomitantly, 7 had somnolence and 3 had dizziness.

RELATIONSHIPS BETWEEN THE FACTORS ASSOCIATED WITH THE INCIDENCE OF CNS SYMPTOMS

Among 17 patients co-treated with opioid analgesics, 2, 4, and 11 patients had GPS of 0, 1, and 2, respectively. These co-treated patients had significantly lower serum levels of albumin ($p = 0.01$) and higher absolute values of plasma pregabalin concentrations ($p = 0.04$, Appendix Figure 2) than patients on pregabalin alone. Of note, the pregabalin dose tended to

be higher in the co-treated patients than in the others although it did not show a significant difference ($p = 0.07$). No significant difference was detected in the absolute value of plasma pregabalin concentrations between patients with and without CNS symptoms ($p = 0.48$) and among the GPS groups ($p = 0.13$). The absolute values of plasma pregabalin concentrations was not correlated with the serum levels of albumin ($R^2 = 0.02$, $p = 0.25$).

Discussion

This study provides information on several clinical factors which influence the variation in plasma pregabalin levels and the incidence of CNS symptoms in cancer patients. The steady-state trough plasma pregabalin concentrations in cancer patients was related to the degree of systemic inflammation status, and opioid analgesic co-treatment in addition to eGFR. Cachectic cancer patients receiving pregabalin and opioid analgesics concomitantly had a higher incidence of CNS symptoms. Thus, advanced cachexia and concomitant use of opioid analgesics were identified as clinical factors which potentially increase the risk of CNS symptoms in pregabalin-treated cancer patients. To the best of our knowledge, this study is the first report demonstrating the impact of cachexia scoring and opioid analgesic co-treatment on the risk of CNS symptoms in cancer patients using pregabalin.

Randinitis et al. reported that the total clearance of pregabalin was 56% of the creatinine clearance in healthy volunteers.[5] A similar association between creatinine clearance with the total clearance of pregabalin was observed in patients with diabetic peripheral neuropathy.[24] However, our regression analysis in cancer patients showed that only 25% of the interindividual variation in plasma pregabalin can be explained by the eGFR, meaning that 75% of the variation is unexplained. This decreased apparent value in cancer patients might be due to the presence of other clinical factors which alter the plasma concentration of pregabalin and the limitation of estimated GFR based on serum creatinine in complicated cancer patients.

The serum level of CRP was detected as one of the factors influencing the plasma pregabalin exposure in this study. High serum CRP levels are reported to be a factor related to renal dysfunction in pre-dialysis patients with chronic renal failure.[25] Cvan Trobec et al. showed that the progressive development of cachexia reduced renal drug elimination in rats.[15] These reports suggest that patients with a higher GPS have a higher CRP, which results in metabolic changes by systemic inflammation. Our observation in cancer patients was consistent with the previous findings.

Eckhardt et al. reported that the increased plasma exposure of gabapentinoid was associated with reduced intestinal motility caused by opioid analgesic co-treatment in healthy volunteers.[26] In contrast, Jokinen et al. demonstrated that opioid analgesics did not alter the pregabalin pharmacokinetics.[27] In the present study, the percentages of patients treated with opioid analgesics in GPS 0, 1, and 2 were 8%, 22%, and 45%, respectively. Patients co-treated with opioid analgesics had higher serum CRP levels which increases GPS. Thus, the concomitant use of opioid analgesics had collinearity with serum CRP levels and GPS. Based on our data, inflammation-related factors might be more responsible than opioid analgesic co-treatment for the elevated plasma concentrations of pregabalin in cancer patients.

Regarding the relationship between inflammation and pharmacokinetics, a possible explanation is that some proinflammatory cytokines influence the pharmacokinetics through an altered expression of drug transporters. Cancer cachexia elevates serum proinflammatory cytokines such as IL-6, TNF-α, and interleukin-1β in addition to the serum level of CRP.[13] In *vitro* study, high concentrations of serum proinflammatory cytokines increased the expression of organic cation transporter 1 (OCTN1) which is widely expressed in human tissues.[28] OCTN1 is considered to be a transporter which contributes to the pharmacokinetics of gabapentinoids including pregabalin.[29,30] These reports imply that systemic inflammation in cancer patients affects pregabalin pharmacokinetics through increased OCTN1 expression in

the kidney.

The authors first hypothesized that elevated plasma pregabalin exposure could be the main reason for the increased incidence of CNS symptoms caused by pregabalin treatment in cancer patients and then detected pre-dose plasma concentrations of pregabalin at steady-state. However, the absolute value of plasma pregabalin concentrations was not directly associated with the incidence of CNS symptoms in this study. This observation was consistent with a previous report that no dose-response pattern with pregabalin was observed in the onset of somnolence and dizziness.[6] However, a dose-response relationship of pregabalin was observed in patients with neuropathic pain.[12] Based on these observations, the neuropsychiatric adverse effects of pregabalin might be due to different mechanisms of the neuropathic pain relief regardless of plasma levels, resulting in these inconsistent observations.

Among 17 patients treated with pregabalin and opioid analgesics concomitantly, 7 had somnolence (41%) and 3 had dizziness (18%). An earlier study also indicated the co-treatment of opioid analgesics as a risk factor for the incidence of somnolence and dizziness in pregabalin-treated patients.[11] Another study in neuropathic pain patients given pregabalin monotherapy (75 mg twice-daily) reported that 11% had somnolence and 17% had dizziness.[12] On the other hand, in patients with opioid analgesic monotherapy, the incidences of somnolence and dizziness were 21% and 22%, respectively.[31] Regarding somnolence, the present study in cancer patients co-treated with pregabalin and opioid analgesics might demonstrate additive or synergetic effects of the two drugs on the CNS symptoms.

Earlier studies reported that cancer patients with advanced cachexia had neuropsychiatric adverse effects with inflammation-related metabolic changes.[14,17,32] Cancer patients with lower serum albumin and higher serum CRP (cf. GPS 2) were likely to be at high risk for the CNS symptoms. Regarding the possible mechanism, the enhanced permeability of the blood-

brain barrier [33,34] linked with proinflammatory cytokines like elevated levels of plasma IL-6 has been discussed.[35,36] In fact, the hyperpermeability of the blood-brain barrier causes cerebral edema and the enhancement of drug brain migration.[37] This could be one of the reasons why patients with GPS 2 had a higher incidence of neuropsychiatric adverse effects without enhanced systemic pregabalin concentration.

Our study has a few limitations. First, this study focused on patients with cancer pain. Therefore, the applicability of our findings to non-cancer pain patients is unclear. Our results need to be applied carefully to non-cancer patients. Second, each GFR value was estimated (eGFR), based on serum creatinine, as a marker of renal function but was not directly measured in this study. The eGFR might not be accurately estimated in advanced cachexia patients with a low serum level of creatinine. Observations using the more applicable method for the evaluation of renal function would help clarify other clinical factors influencing the plasma concentration of pregabalin and incidence of adverse effects. Third, cachexia was assessed using an inflammation-based cachexia score, GPS, but not a clinical symptoms-based cachexia score which evaluates the loss of body weight or body mass index.[38] This is unlikely to matter for our findings since our previous study demonstrated that GPS could be substituted for the clinical symptoms-based cachexia score.[35] Although the GPS does not use body weight loss or change in body mass index for assessing cachexia status, it is sufficient to classify the inflammation-related cachexia severity. Forth, this study is an observational study. Thus, patients who developed CNS symptoms cannot be identified unless described in the medical record. However, specialists in palliative care and pain management evaluated and recorded the CNS symptoms frequently in our hospital. A further prospective study which allows for collection of plasma samples for concentration measurements immediately after the CNS symptoms would clarify the association between symptoms and plasma concentrations of pregabalin.

In the present study, although the absolute value of plasma pregabalin concentrations was not strongly associated with the incidence of CNS symptoms, cachexia-related inflammation and opioid analgesics were identified as potential factors influencing the steady-state trough plasma concentration and CNS symptoms of pregabalin. Evaluation of cachexia scoring and opioid analgesics co-treatment in addition to renal function may be useful for a proactive assessment for the risk of adverse events such as CNS symptoms during the treatment of pain in cancer patients.

Conclusions

In cancer patients, the steady-state trough plasma pregabalin concentrations was altered with renal function, systemic inflammation, and opioid analgesic co-treatment. Whereas, a higher incidence of CNS symptoms observed in cancer patients on pregabalin related more to cachexia and opioid analgesic co-treatment than to altered pregabalin concentrations. For these patients, the pregabalin dose needs to be carefully adjusted from the viewpoint of safety.

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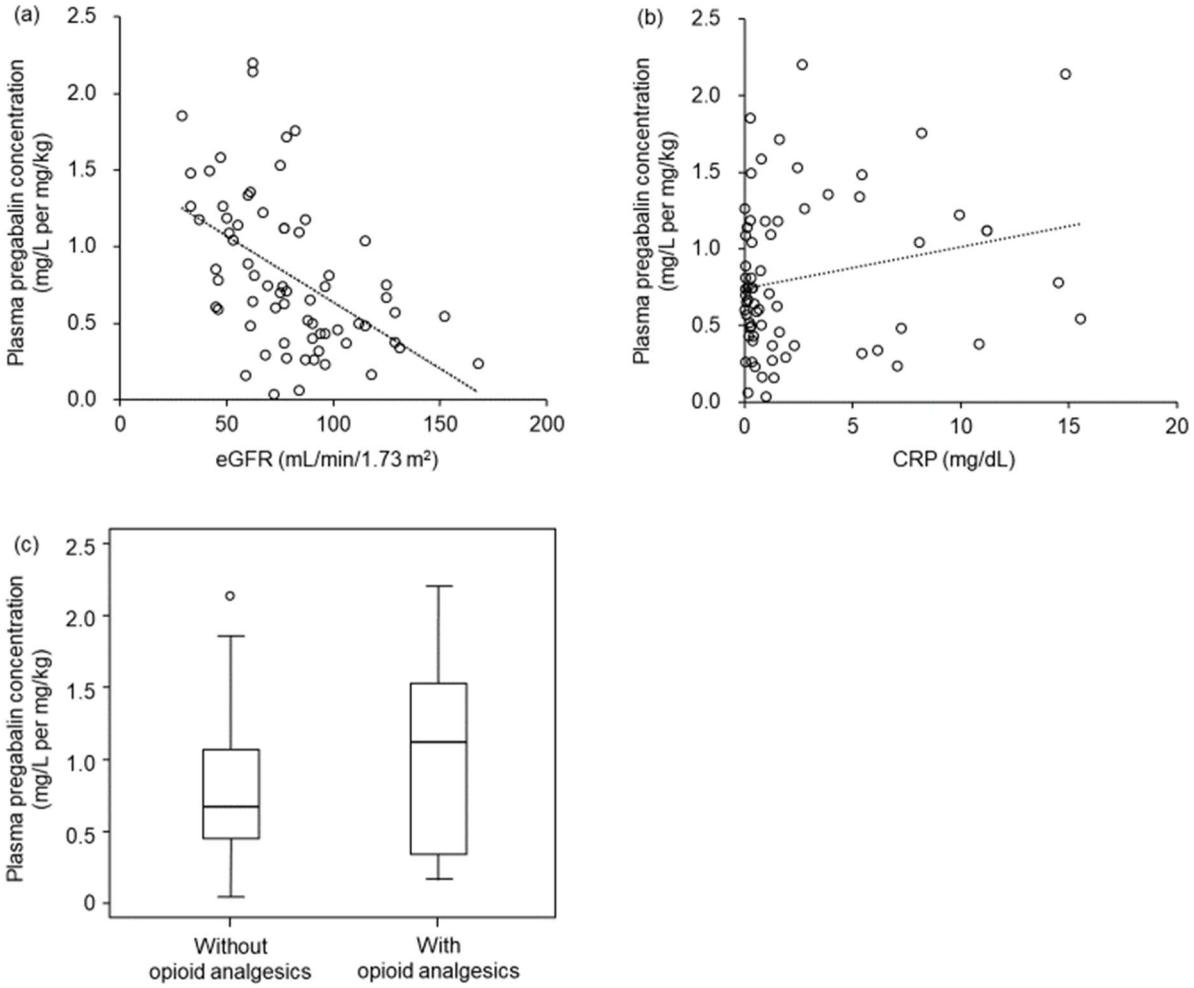
Figure 1: Relationships between clinical factors and the steady-state trough plasma pregabalin concentrations in cancer patients.

a) estimated glomerular filtration rate, **b)** C-reactive protein concentrations, and **c)** patients co-treated with or without opioid analgesics. The statistics were analyzed using Pearson's test and the Mann-Whitney *U* test. The box plot shows the 25th and 75th percentiles, median (thick line), and outliers (circles) of the steady-state trough plasma pregabalin concentrations.



Appendix, Figure 2: Relationships between clinical factors and the absolute values of plasma pregabalin concentrations in cancer patients.

a) patients co-treated with or without opioid analgesics, **b)** Glasgow Prognostic Score (GPS), and **c)** serum albumin concentrations. The statistics used for a, b, and c were the Mann-Whitney *U* test, Kruskal-Wallis test, and Pearson's test, respectively. The box plots show the 25th and 75th percentiles, median (thick line), and outliers (circles) of the absolute value of plasma pregabalin concentration.

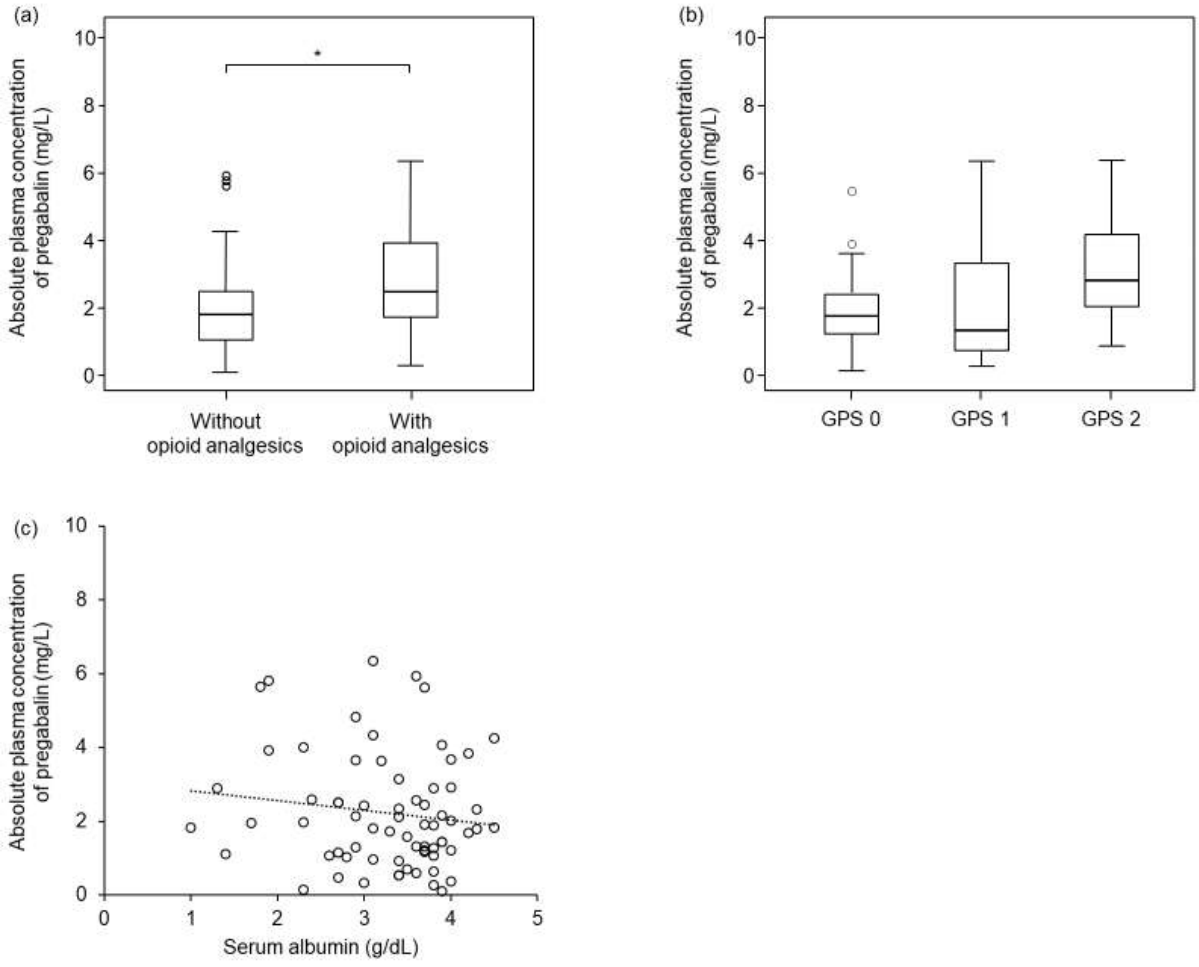


Table1 Patient characteristics

		Glasgow Prognostic Score		
	Total (n = 68)	0 (n = 26)	1 (n = 18)	2 (n = 24)
Gender, male/female	45/23	14/12	13/5	18/6
Age, years	66 (56–74)	56 (43–66)	74 (66–78) **	68 (58–75) *
Body weight, kg	56.1 (47.1–62.8)	58.5 (48.9–63.4)	49.2 (42.2–56.0) *	58.2 (48.9–67.2)
Body mass index, kg/m^2	20.8 (19.3–24.8)	21.0 (19.4–25.7)	19.9 (18.7–20.9)	21.7 (19.3–25.4)
Serum creatinine, mg/dL	0.75 (0.50–0.90)	0.75 (0.58–0.93)	0.82 (0.63–1.1)	0.73 (0.54–0.80)
eGFR, mL/min/1.73 m^2	77.0 (66.0–94.5)	75.5 (56.3–95.5)	70.5 (47.8–87.7)	78.0 (67.8–103) #
Total protein, g/dL	6.3 (5.8–6.7)	6.6 (6.2–6.9)	6.4 (5.7–6.7)	5.9 (5.3–6.4)
Serum albumin, g/dL	3.4 (2.9–3.8)	3.9 (3.7–4.0)	3.4 (3.1–3.6) *	2.7 (1.9–3.0) **
C-reactive protein, mg/dL	0.77 (0.25–2.7)	0.24 (0.05–0.35)	0.75 (0.29–1.3) **	5.4 (1.8–8.1) **
Total bilirubin, mg/dL	0.5 (0.3–0.9)	0.5 (0.4–0.9)	0.4 (0.3–0.7)	0.6 (0.4–0.8)
Aspartate transaminase, U/L	22 (16–26)	20 (16–26)	19 (16–24)	17 (13–22)
Alanine transaminase, U/L	18 (13–30)	22 (16–28)	16 (10–23)	24 (14–30)
Concomitant use of opioid	17	2	4	11
Pregabalin dose, mg twice daily	25–200	25–200	25–150	25–150

Data are expressed as number or median and interquartile range in parentheses. Pregabalin dose was expressed as range.

eGFR, estimated glomerular filtration rate.

*$p < 0.05$ and **$p < 0.01$, different from the Glasgow Prognostic Score 0 group.

# $p < 0.05$, different from the Glasgow Prognostic Score 1 group.

Table 2 Factors related to the steady-state trough plasma pregabalin concentration in cancer patients

	Simple linear regression		Multiple linear regression	
	R^2	p value	β	p value
eGFR, mL/min/1.73 m^2	0.25	< 0.01	-0.60	< 0.01
Age, years	0.02	0.25	–	0.53
Serum albumin, g/dL	0.01	0.39	–	0.74
C-reactive protein, mg/dL	0.05	0.08	0.31	< 0.01
	Comparison of median			
Concomitant use of opioid analgesics	–	0.27	0.24	0.02
Gender	–	0.14	–	0.51
Glasgow Prognostic Score	–	0.40	–	–

eGFR, estimated glomerular filtration rate; R2, coefficient of determination; and β, standardized partial regression coefficient.

Table 3 Factors related to the central nervous system symptoms in cancer patients treated with pregabalin

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Absolute pregabalin concentration, mg/L	–	0.42	–	0.99
Body weight, kg	–	0.09	–	–
Body mass index, kg/m^2	–	0.28	–	–
eGFR, mL/min	–	0.36	–	0.86
Age, years	–	0.78	–	0.55
Serum albumin, g/dL	0.49 (0.25–0.95)	0.04	–	–
C-reactive protein, mg/dL	–	0.31	–	–
Concomitant use of opioid analgesics	7.0 (2.1–24)	< 0.01	7.0 (2.1–24)	< 0.01
Gender	–	0.07	–	0.12
Glasgow Prognostic Score	2.2 (1.2–4.2)	0.01	–	0.12

eGFR, estimated glomerular filtration rate; OR, odds ratio; and CI, confidence interval.