



Population pharmacokinetics of palonosetron and model-based assessment of dosing strategies

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Abstract

Purpose Palonosetron is the most recent 5-hydroxytryptamine-3 receptor antagonist, and its fixed dose of 0.075 mg is indicated for the prevention of postoperative nausea and vomiting. This study aimed to examine whether fixed dosing is more appropriate than body size-based dosing through the development of a population pharmacokinetic model and model-based simulations.

Methods Fifty-one adult patients undergoing general anesthesia received single intravenous palonosetron administrations 30 min before the end of surgery. Palonosetron concentrations were measured in blood samples collected at various time-points within 48 h. A population pharmacokinetic analysis was performed by non-linear mixed-effects modeling, and the area under the curves (AUCs) for fixed dosing and body size-based dosing were simulated.

Results The pharmacokinetics of palonosetron were best described by the three-compartment model, and lean body weight (LBW) was the most significant covariate for all pharmacokinetic parameters. In a patient with LBW of 40 kg, typical clearance and central volume of distribution were 0.102 L/min and 6.98 L, respectively. In simulations, the overall interindividual variability in AUC (0, 48 h) of fixed dosing was not much higher than that of body size-based dosing. In subgroup analysis, the AUCs (0, 48 h) of fixed dosing were considerably lower in the high-weight subgroup and higher in the low-weight subgroup than the median-weight subgroup. In contrast, LBW-based dosing showed similar AUC distributions among the three subgroups.

Conclusion LBW-based dosing might be suitable for high-weight patients to avoid possible underdosing. Nevertheless, the current fixed dosing of palonosetron is acceptable for adult patients with normal weight.

Keywords Palonosetron · Pharmacokinetics · PONV

Introduction

Postoperative nausea and vomiting (PONV) affects the economics of medical care, as well as patient satisfaction and quality of life [1]. For the prophylaxis and treatment of PONV, 5-hydroxytryptamine-3 receptor (5-HT₃) antagonists have been used with increasing frequency over the last two decades, and improved agents with higher efficacy and longer activity have been introduced. However, single-drug

treatment with a 5-HT₃ antagonist fails to prevent PONV in some surgical patients, even those at low risk of PONV.

The etiology of PONV is multi-factorial; this may be a major cause for unsuccessful responses to a single 5-HT₃ antagonist [2, 3]. However, interindividual variability in pharmacokinetics is another potential explanation for the unsuccessful response. Dose–concentration relationships can be influenced by certain patient demographic, pathophysiological, and therapeutic factors, including body weight, metabolic functions, and concurrent medications [4, 5]. There are also concerns regarding possible overdosing and underdosing due to the current fixed-dosing strategy for 5-HT₃ antagonists [6].

Population pharmacokinetic modeling is a useful tool to describe interindividual variability and to identify measurable factors (“covariates”) that cause changes in the dose–concentration relationship [5, 7]. It can also simulate

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systemic exposure [represented by the area under the curve (AUC)] following different dosing strategies. However, population pharmacokinetic studies of recently developed 5-HT₃ antagonists are limited despite their frequent clinical use.

Palonosetron (Aloxi[®]; Helsinn Healthcare, Lugano, Switzerland), a second-generation 5-HT₃ antagonist, was initially approved in 2003 for the prevention of chemotherapy-induced nausea and vomiting; the fixed dose of 0.075 mg is now also indicated for the prevention of PONV in many countries, including the United States and South Korea. Several traditional pharmacokinetic studies of palonosetron have been performed in healthy volunteers [8–10] and cancer patients [11]. After intravenous dosing with palonosetron, the initial rapid and extensive distribution is followed by a slow elimination phase. This slow elimination results in a half-life of about 40 h [8–11], which is longer than the 4–9-h half-life of first-generation 5-HT₃ antagonists, such as ondansetron. Palonosetron shows linear pharmacokinetics with dose-dependent increases in AUC [9, 11], and its pharmacokinetic characteristics are not affected by age, hepatic impairment, and mild to moderate renal impairment according to prescribing information [12]. However, the impact of body size [e.g., total body weight and lean body weight (LBW)] on the pharmacokinetics of palonosetron remains unclear, although it is generally believed that body size-based dosing would reduce any interindividual variability in the pharmacokinetics of a drug. The objective of this pharmacokinetic study was to examine whether fixed dosing is more appropriate than body size-based dosing through the development of a population pharmacokinetic model of intravenous palonosetron in adult surgical patients.

Patients and methods

The study was approved by our local institutional review board, and was registered with the Clinical Research Information Service, Republic of Korea (<https://cris.nih.go.kr>), prior to patient enrollment under registration number KCT0001254.

A convenience sample of 51 patients participated in this pharmacokinetic study, and written informed consent was obtained from all patients as per the Declaration of Helsinki. Patients aged 19–80 years (ASA Physical Status I or II) who were scheduled for elective surgery under general anesthesia were included. Patients with the following were excluded: history of recent intake of selective serotonin reuptake inhibitors; any history of hepatic or renal disease; abnormal laboratory findings; or an allergy to 5-HT₃ antagonists.

General anesthesia was induced with propofol (2 mg/kg) and remifentanyl (1 µg/kg), and tracheal intubation was facilitated by rocuronium (0.8 mg/kg). Anesthesia was

subsequently maintained with a sevoflurane and remifentanyl infusion to achieve bispectral index values of 40–50. Pyridostigmine and glycopyrrolate were used for reversal of the neuromuscular blockade at the end of surgery. After surgery, all patients received the same regimen of intravenous patient-controlled analgesia (IV-PCA) for 48 h. The IV-PCA device contained 100 mL saline with 1500 µg fentanyl and 180 mg ketorolac; basal infusion rate was 1 mL/h, and a patient-controlled dose was 1 mL with a lockout time of 15 min. PONV episodes were assessed by an independent research nurse at 1, 6, 24, and 48 h postoperatively.

Patients were assigned randomly to receive a single bolus of 0.075, 0.15, or 0.225 mg of palonosetron intravenously about 30 min before the end of surgery ($n = 17$ for each dose). Randomization was performed using a computer-derived random number sequence. The patients and all researchers involved in this study were blinded to the treatment assignment. The lowest dose was 0.075 mg (recommended dose for PONV) and the highest dose was 0.225 mg; the latter was chosen for safety considerations (based on the recommended dose of 0.25 mg for chemotherapy-induced nausea and vomiting). Arterial blood samples (5 mL) were collected immediately before the administration of palonosetron (0 min), at 2, 5, 10, 15, and 30 min, and 1, 2, 6, 24, and 48 h after the administration of palonosetron. After centrifugation (3000 rpm, 10 min), all plasma samples were transferred to polyethylene tubes and stored at -70°C until assayed.

Drug quantification

A high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was performed to determine plasma concentrations of palonosetron. Briefly, each 200-µL plasma sample was mixed with 20 µL of 5 ng/mL risperidone and 20 µL of 0.1 N sodium hydroxide; to each sample, 1 mL of methyl tert-butyl ether was added. The mixture was vortexed for 1 min and centrifuged for 2 min (12,000 rpm). Then, the supernatant was transferred to a new tube and evaporated under a stream of nitrogen at 40°C . The residue was reconstituted in 100 µL of 20% methanol, and 10 µL of the sample was injected into the LC-MS/MS system [LC system: Shimadzu LC-20A (Shimadzu Co., Kyoto, Japan); MS/MS system: API 4000Q TRAP (AB SCIEX, Framingham, MA, USA)]. In the LC system, a Gemini C18, 3.0 µm, 500 × 2.0 mm (Phenomenex, Torrance, CA, USA) column was used, and the mobile phase consisted of methanol and distilled water (55:45, v/v) with 0.1% formic acid and 10 mM ammonium acetate. The flow rate was maintained at 200 µL/min. The linear calibration curve for palonosetron was validated in the range of 0.02–50 ng/mL ($r^2 = 0.98$). The precision (coefficients of variation) and accuracy (relative errors of the mean) of

intra- and inter-day analyses were verified to be within 15% and 85–115%, respectively.

Population pharmacokinetic analysis

For the population pharmacokinetic analysis, non-linear mixed-effects modeling was performed in NONMEM 7.3 (ICON Developmental Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method with the interaction option. The term “mixed-effects” is used because it allows both fixed and random effects to be modeled simultaneously. A fixed-effect parameter represents a typical mean value for the population (θ_{TV}), which is identical for all individuals. The variance of the differences between the typical values and each individual parameter value describes interindividual variability [expressed as the coefficient of variation (%CV)], which is estimated as a random-effect parameter. Additionally, the variance of the differences between measured concentrations and predicted concentrations from the model describes residual errors at the observational level, which is estimated as another random-effect parameter. The one-, two-, and three-compartment models were assessed when selecting a base structural model. Interindividual variability was modeled using an exponential model, and residual error was modeled using a proportional error model.

To evaluate the impact of covariates on pharmacokinetic parameters, all potential covariates [i.e., age, sex, height, total body weight (TBW), LBW [13], body surface area [14], ideal body weight [15], adjusted body weight [16], and body mass index (BMI)] were added to the base model separately using different functions: linear, power, exponential, and allometric. LBW was calculated by the Janmahasatian formula: $(9270 \times TBW)/(6680 + 216 \times BMI)$ for men $(9270 \times TBW)/(8780 + 244 \times BMI)$ for women. Ideal body weight was calculated by the Devine formula: $50 + 0.9 \times (\text{height} - 152)$ for men, $45.5 + 0.9 \times (\text{height} - 152)$ for women.

The comparisons of alternative structural models and the inclusion of covariates were based on a likelihood ratio test with NONMEM's objective function value (OFV). A difference in OFV between models of > 6.63 was considered statistically significant with a p value < 0.01 (approximate chi-squared distribution with one degree of freedom) [17]. The exclusion of interindividual variability terms on each pharmacokinetic parameter was also evaluated based on the difference in OFV in the same manner. For all models, model misspecification was assessed by standard diagnostic goodness-of-fit plots [18], including the population-predicted concentrations (PRED; predicted from the population PK model) or the individual-predicted concentrations (IPRED; predicted from the individual post hoc Bayesian PK parameter estimates) vs. measured concentrations, and the population conditional weighted residuals (CWRES) vs.

PRED or time. If a good model fit is obtained, PRED and IPRED values are close to the measured concentrations with no obvious biases, and CWRES values between -2 and $+2$ are the expected standard deviations around a mean of zero.

The reliability and stability of the final model were evaluated by nonparametric bootstrap analysis using fit4NM (v. 3.5.1, <https://www.fit4nm.org/download>; Eun-Kyung Lee and Gyu-Jeong Noh, Seoul, South Korea) [19]. In total, 2000 bootstrap replicate data sets were generated from the original data set by random sampling with replacement. The median values and the 95% confidence intervals of parameter estimates from the bootstrap replicates were compared with the final model. The predictive performance of the final model was evaluated using the visual predictive check implemented in Pearl-speaks-NONMEM (PsN, v. 4.7.0) [20, 21]. The visual predictive check was based on 2000 simulated concentration–time profiles of the final model and contained all measured palonosetron concentrations as well as the corresponding 5th, 50th (median), and 95th percentiles of the model-predicted concentrations.

Pharmacokinetic simulation

To explore the possible implications of the final population pharmacokinetic model further, Monte Carlo simulations for fixed dosing and body size-based dosing were conducted using NONMEM. Individual post hoc pharmacokinetic parameters were generated for each virtual subject, and the individually predicted concentration–time profiles were obtained for each dosing strategy. Consequently, the AUC (0, 48h) values were determined by linear trapezoidal integration over the 0–48 h after drug administration. The mean value of body size in virtual subjects was used as the conversion factor for dose determinations so that the mean dose in the body size-based dosing was similar to the fixed dose. The values of influential covariates for virtual subjects were generated randomly assuming a normal distribution with a similar mean and standard deviation to the original study population.

R version 3.4.4 (the R foundation for Statistical Computing) and SigmaPlot 12.5 (Systat Software Inc., San Jose, CA, USA) were used for statistical analyses and graph generation.

Results

In total, 519 palonosetron plasma samples from 51 adult surgical patients were used for population pharmacokinetic modeling. Concentrations below the lower limit of quantification ($0.02 \mu\text{g/mL}$) were not detected after drug administration. The demographic characteristics of the patients are summarized in Table 1.

Table 1 Characteristics of patients receiving palonosetron for population pharmacokinetic analysis

Characteristics	Total (<i>n</i> = 51)	0.075 mg (<i>n</i> = 17)	0.15 mg (<i>n</i> = 17)	0.225 mg (<i>n</i> = 17)
Gender, male/female	21/30	5/12	7/10	9/8
Age, years	59.2 (9.7)	58.7 (9.4)	59.7 (11.5)	59.2 (8.7)
Height, cm	160.3 (7.3)	159.7 (6.8)	158.4 (7.6)	162.7 (7.3)
Total body weight, kg	62.7 (10.1)	63.7 (10.4)	59.3 (8.2)	65.2 (11.2)
Lean body weight, kg	43.4 (8.7)	42.5 (8.8)	41.4 (6.9)	46.1 (9.8)
Body mass index, kg/m ²	24.4 (3.7)	25.0 (3.8)	23.7 (4.1)	24.6 (3.4)
No. of blood samples	10.2 (1.2)	10.3 (0.8)	10.1 (1.5)	10.1 (1.2)
Type of surgery				
Gastrectomy (laparoscopic/open)	16/3	4/1	6/1	6/1
Hysterectomy (laparoscopic/open)	13/3	6/1	4/2	3/0
Colectomy (laparoscopic/open)	16/0	5/0	4/0	7/0

Values are mean (SD) or number of patients

LBW lean body weight calculated using the Janmahasatian formula

Both two- and three-compartment models were fitted to the data. However, the two-compartment model showed noticeable bias in plots of residual vs. time, especially in the early phase with high palonosetron concentrations. Thus, the three-compartment model was selected, and the concentrations predicted by this model were mostly fitted to the observed concentrations for the entire time period (Fig. 1). The three-compartment model was parameterized in terms of the central volume of distribution (V_1), rapid peripheral volume of distribution (V_2), slow peripheral volume of distribution (V_3), metabolic clearance (CL), inter-compartmental clearance of rapid peripheral compartments (Q_1), and inter-compartmental clearance of rapid peripheral compartments (Q_2). The removal of interindividual variability terms for V_2 and Q_1 did not result in a significant difference in the objective function; therefore, they were excluded in the final step. During the covariate analysis for the body-size predictors, the allometric function showed a better fit than the linear, power, or exponential function.

LBW was the most significant covariate affecting pharmacokinetics of palonosetron in the covariate analysis. The pharmacokinetic parameter estimates of the three-compartment base model and competing covariate models are presented in Table 2, together with the OFV and interindividual variability values. Compared with the base model (with no covariate), TBW improved the model fit considerably (Model A1), and incorporation of height as a covariate on Q_2 further improved the model fit (Model A2). However, Model B with a sole covariate (i.e., LBW) gave similar pharmacokinetic parameters, interindividual variability, OFV, and diagnostic plots as did Model A2. Age and sex showed no significant influence on any pharmacokinetic parameter during the covariate analysis. Thus, Model B was selected as the final population pharmacokinetic model for palonosetron due to its simplicity (one less parameter). The

interindividual variability (%CV) of each pharmacokinetic parameter in the final model showed an overall decrease, especially in V_1 , from 46.6% in the base model to 27.4% in the final model (i.e., a relative decrease of 41.2%).

The goodness-of-fit plots for the final model showed adequate model performance (Fig. 1). The relationship between the measured vs. predicted concentrations demonstrated that the predictions were unbiased and appropriate for the population and the individual patients in this study (Fig. 1a, b). Plots of CWRES against population-predicted concentrations or time evenly distributed around zero, indicating no systemic bias in the structural or residual error models (Fig. 1c, d). As shown in Table 3, the relative standard error for each fixed-effect parameter was < 30%, indicating acceptable precision of the parameter estimates [22]. In addition, the median parameter estimates resulting from the nonparametric bootstrap were reasonably close (within 10%) to the respective parameter estimates from the final model, indicating good reliability and stability of the final model [23]. In a visual predictive check (Fig. 2), dose-normalized measured concentrations were overlaid with the 90% prediction intervals of the model-predicted plasma concentrations. The results suggest that the final model reproduced both the central tendency and the variability of the measured palonosetron concentration–time profile.

Plasma palonosetron concentrations for 1000 virtual subjects were simulated from the final model using a fixed (0.075 mg), TBW-based (0.0012 mg/kg), and LBW-based (0.0017 mg/kg) dose. For the virtual subjects, interindividual variabilities (%CV) for the AUC (0, 48 h) after each dosing method were similar (23.9% after fixed dosing, 21.4% after TBW-based dosing, and 19.1% after LBW-based dosing). To determine the influence of body size for each dosing method, the AUC (0, 48 h) values of three weight subgroups were compared (Fig. 3): low-weight group (*n* = 100,

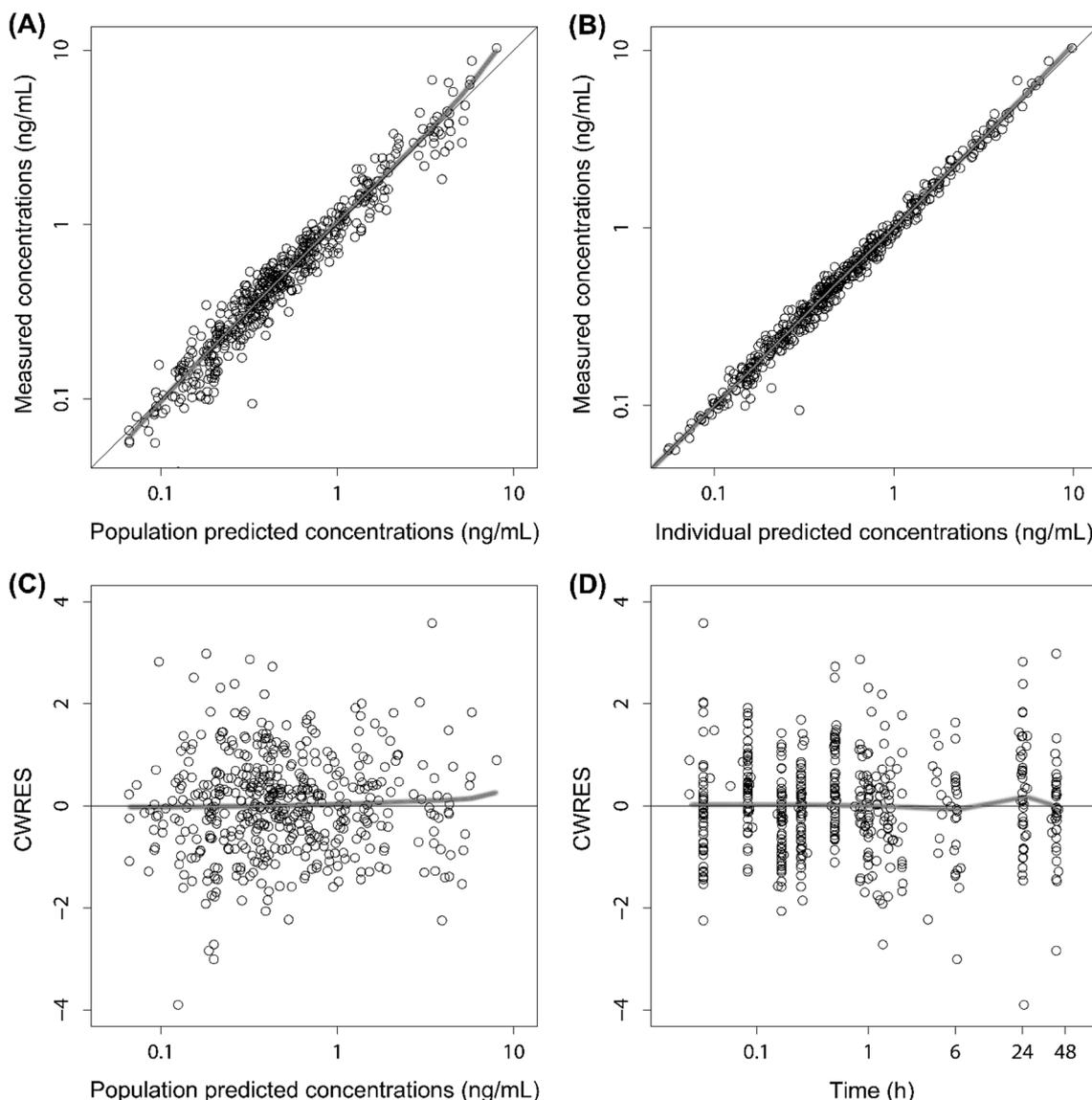


Fig. 1 Goodness-of-fit plots. Measured vs. **a** population- or **b** individual-predicted palonosetron concentrations. The solid line is the line of identity. Conditional weighted residuals (CWRES) vs. **c** population-

predicted palonosetron concentrations or **d** time. The gray bold line is a LOWESS (locally weighted scatterplot smoothing) fit to the data

TBW 43.3 ± 4.3 kg, below 10th percentile), median-weight group ($n = 100$, TBW 62.5 ± 0.8 kg, 46–55th percentile) and high-weight group ($n = 100$, TBW 79.8 ± 3.7 kg, above 90th percentile). Fixed dosing tended to result in lower AUC (0, 48 h) for the high-weight group and greater AUC (0, 48 h) for the low-weight group compared to the AUC (0, 48 h) for the median-weight group ($p < 0.001$, ANOVA), although LBW-based dosing showed similar AUC (0, 48 h) distributions for the three weight subgroups ($p = 0.129$, ANOVA).

Data related with prophylactic efficacy of palonosetron were also collected in this pharmacokinetic study despite the small sample size ($n = 17$ for each dose group). The rates of complete response (no PONV and no rescue

therapy) until 48 h after surgery were 41.2, 58.8, and 64.7% in the 0.075, 0.15, and 0.225 mg groups, respectively ($p = 0.172$, linear by linear association). PONV risk scores (female = 1, prior history of PONV or motion sickness = 1, non-smoking = 1, the use of postoperative opioids = 1) were similar between groups (3.1 ± 0.9 , 3.0 ± 0.8 , and 2.9 ± 0.9 ; $p = 0.695$, Kruskal–Wallis), and AUC (0, 48 h) increased proportionally to the dose (322.5 ± 96.1 , 683.2 ± 263.4 , and 1018.7 ± 413.8 ng/min/mL; $p < 0.001$, ANOVA). Rescue antiemetics were administered to three patients in the 0.075 mg group and to one patient in the 0.15 mg group. No treatment-related adverse event, including headache and constipation, was observed in the present study.

Table 2 Comparison of pharmacokinetic parameters between four competing models of palonosetron

	Base model	Model A1	Model A2	Model B (final model)
Covariate	None	TBW	TBW, height	LBW
OFV	−1741.0	−1778.3	−1789.4	−1788.4
Pharmacokinetic parameter				
V_1 (L)	10.6	$7.99 \times (\text{TBW}/60)$	$7.22 \times (\text{TBW}/60)$	$6.98 \times (\text{LBW}/40)$
V_2 (L)	19.2	$16.5 \times (\text{TBW}/60)$	$15.6 \times (\text{TBW}/60)$	$15.2 \times (\text{LBW}/40)$
V_3 (L)	388	$377 \times (\text{TBW}/60)$	$377 \times (\text{TBW}/60)$	$365 \times (\text{LBW}/40)$
CL (L/min)	0.105	$0.104 \times (\text{TBW}/60)^{0.75}$	$0.104 \times (\text{TBW}/60)^{0.75}$	$0.102 \times (\text{LBW}/40)^{0.75}$
Q_1 (L/min)	3.28	$3.18 \times (\text{TBW}/60)^{0.75}$	$3.08 \times (\text{TBW}/60)^{0.75}$	$3.06 \times (\text{LBW}/40)^{0.75}$
Q_2 (L/min)	4.82	$4.57 \times (\text{TBW}/60)^{0.75}$	$4.5 \times (\text{TBW}/60)^{0.75} + (\text{height} - 160) \times 0.0542$	$4.39 \times (\text{LBW}/40)^{0.75}$
Interindividual variability (%CV)				
V_1	46.6	34.5	27.1	27.4
V_3	24.6	17.7	17.3	18.4
CL	39.4	38.5	38.2	35.5
Q_2	23.1	18.1	15.4	15.7
Residual error				
Proportional (%)	12.6	13.0	13.2	13.2

TBW total body weight, LBW lean body weight, OFV objective function value (−2 log likelihood), V_1 central volume of distribution, V_2 rapid peripheral volume of distribution, V_3 slow peripheral volume of distribution, CL metabolic clearance, Q_1 inter-compartmental clearance of rapid peripheral compartment, Q_2 inter-compartmental clearance of slow peripheral compartment, CV coefficient of variation

Table 3 Comparison of the results obtained from the final model and the nonparametric bootstrap analysis (BS) with 2000 replicates

	Estimate	%RSE	95% CI (model)	Median (BS)	95% CI (BS)
Fixed-effect parameter (θ_{TV})					
V_1	6.98	29.1	3.00–11.97	7.36	4.03–17.0
V_2	15.2	18.4	9.7–20.7	15.8	10.4–24.0
V_3	365	3.0	343–387	363	343–386
CL	0.102	6.5	0.089–0.115	0.102	0.088–0.114
Q_1	3.06	17.2	2.03–4.09	3.11	1.97–3.96
Q_2	4.39	8.1	3.70–5.09	4.44	3.70–5.15
Interindividual variability (%CV)					
V_1	27.4	45.6	8.1–46.7	29.4	8.5–50.6
V_3	18.4	19.8	14.4–21.7	18.3	14.3–22.0
CL	35.5	42.3	14.7–48.0	33.9	19.1–51.5
Q_2	15.7	24.9	11.2–19.1	15.9	11.9–20.8
Residual error					
Proportional (%)	13.2	7.0	11.4–15.0	12.9	10.9–14.8

V_1, V_2, V_3 (L) = $\theta_{TV} \times (\text{LBW}/40)$; CL, Q_1, Q_2 (L/h) = $\theta_{TV} \times (\text{LBW}/40)^{0.75}$, LBW lean body weight, θ_{TV} typical pharmacokinetic value for a patient with LBW of 40 kg, CV coefficient of variation, %RSE percent relative standard error of the estimate = standard error/parameter estimate \times 100

Discussion

Palonosetron has been used for PONV prophylaxis after the extended approval of the US Federal Drug Administration in 2008. Many studies have demonstrated that palonosetron provides more effective prophylaxis of PONV during the first 24 h after surgery compared with

ondansetron, a first-generation 5-HT₃ antagonist [24]. In a recent meta-analysis [25], 0.075 mg palonosetron showed similar efficacy to 0.3 mg ramosetron for early PONV prevention (for 24 h), and even showed better efficacy for delayed PONV prevention (for 48 h). This fixed dose of 0.075 mg was determined based on early phase III clinical trials [26, 27], and it has been considered as the minimum effective dose of palonosetron for PONV [28]. However,

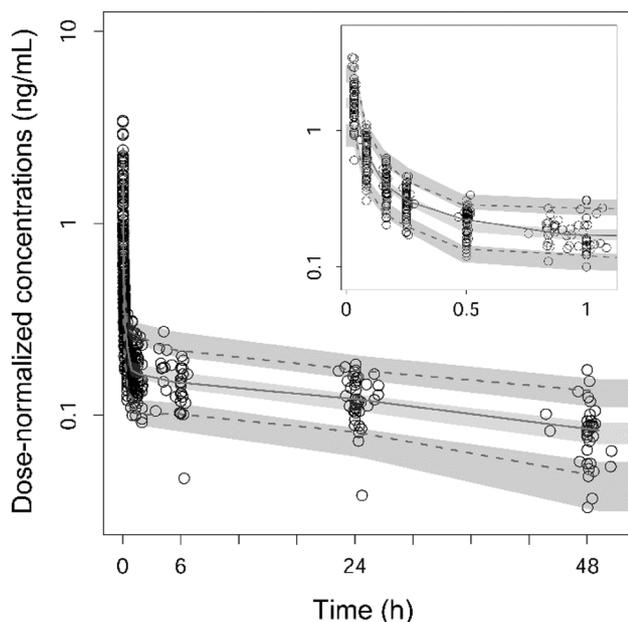


Fig. 2 Visual predictive check of the final population pharmacokinetic model of palonosetron. The solid line denotes the 50th percentile while the dashed lines denote the 5th and 95th percentiles of the observations. The shaded area represents the 95% confidence interval for each percentile of the simulation. The measured concentrations are plotted as open circles

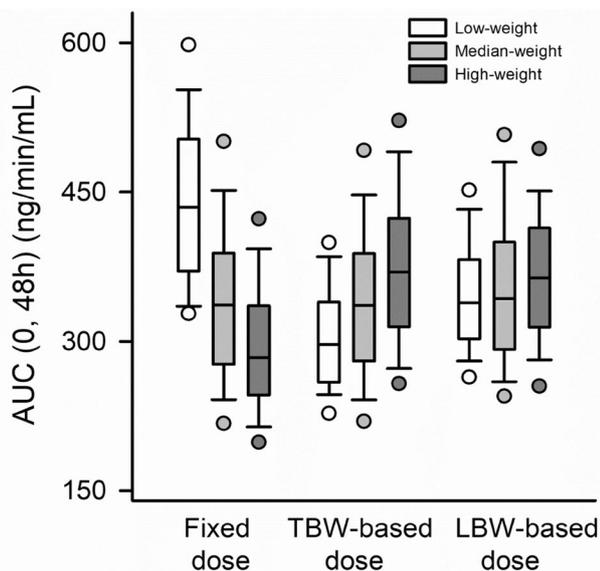


Fig. 3 Box plots of the simulated area under the curve (AUC; 0–48 h) of palonosetron after a fixed, total body weight (TBW)-, or lean body weight (LBW)-based dose for three subgroups with lower 10%, median 10% and upper 10% of TBW for 1000 virtual subjects

pharmacokinetic analysis for the fixed dosing of palonosetron has not been performed previously.

In the present study, patient body size had a significant impact on the pharmacokinetic parameters of palonosetron. Among various body-size descriptors, LBW produced the best model performance and the largest reduction in inter-individual variability as a single covariate. TBW was the second-best covariate after LBW, and the addition of another body-size descriptor, height, made the TBW-scaled model comparable with the LBW-scaled model. This finding demonstrates that the pharmacokinetics of palonosetron were affected not only by weight, but also by height. The calculated LBW used in the final model may simply reflect both weight and height components [13].

Furthermore, the volume of distribution correlates better with LBW than with TBW for water-soluble drugs such as palonosetron [29, 30]. Systemic clearance also correlates well with LBW in drugs eliminated predominantly by the liver [29, 30]. The metabolism of palonosetron takes place primarily in the liver, and is mediated by the cytochrome P450 enzyme system [12, 28].

In the present study, the pharmacokinetics of palonosetron did not significantly depend on other covariates (such as age or sex) as reported previously [12, 31], and considerable interindividual variabilities (%CV) remained unexplained in the final model (V_1 , 27.4%; CL, 35.5%) despite the impact of body size on the pharmacokinetic parameters. In our simulations, the reduction of the AUC variation in the body size-based dosing was also less than expected. Nevertheless, the difference of the AUCs between low-weight and high-weight subgroups suggested the possibility of underdosing in high-weight patients or overdosing in low-weight patients under the fixed dosing strategy (Fig. 3).

Overdosing in low-weight patients may not be of great concern because no clear dose-dependent relationship in the incidence of adverse events, including QT interval prolongation on an electrocardiogram, has been reported [32–34]. In contrast, underdosing of palonosetron in high-weight patients may result in prophylactic failure. Early phase III clinical studies reported that the prophylactic efficacy increased dose-dependently in 0.025, 0.05, and 0.075 mg groups; however, 0.025 and 0.05 mg palonosetron did not produce a significant effect compared with a placebo [26, 27]. Therefore, the fixed dose of 0.075 mg in some high-weight patients could not achieve the therapeutic level of AUCs or plasma concentrations. In the present simulations, the 90th percentile cutoff for the high-weight subgroup (75.9 kg, simulated by the observed distribution) was close to normal weight; therefore, the AUCs in the actual high-weight population, such as obese patients, would be much lower.

To date, no clinical study has demonstrated the efficacy of palonosetron in high-weight patients, and only few

studies have assessed ondansetron in high-weight patients. Bataille et al. [35] reported that conventional fixed doses of ondansetron (4 mg) with dexamethasone (4 mg) was not effective for morbidly obese patients, and they suggested that optimal antiemetic dosage and combination therapies need to be established for obese patients. Conversely, Mendes et al. [36] reported that ondansetron (0.1 mg/kg) with dexamethasone (0.1 mg/kg) was more effective than placebo in obese patients. The contrasting results of the two studies might be associated with the different dosing strategies (fixed vs. body size-based dosing) because body weight was found to be a significant covariate for all pharmacokinetic parameters of ondansetron [37], as in the present study.

Our model-based simulations demonstrated that the overall pharmacokinetic variability after fixed dosing did not differ markedly from that of body size-based dosing. However, the simulations also showed that the current single fixed dosage could result in possible underdosing in high-weight patients. Therefore, body size-based dosing of palonosetron may be considered for high-weight patients if the reduced efficacy of the current fixed dose for the said population is revealed in future studies.

This pharmacokinetic study was not designed to compare the prophylactic efficacy between dose groups; however, there was an interesting finding in the clinical efficacy data of palonosetron. The complete response rates showed an increasing trend over the dose of 0.075 mg (statistically not significant). In 2005, White et al. reported the abstract of a dose-ranging study [38], which demonstrated that only 1 µg/kg and 30 µg/kg of palonosetron produced significant and similar efficacy among 0.1, 0.3, 1, 3, and 30 µg/kg dose groups. From this result, 1 µg/kg (comparable to 0.075 mg) could be understood as the ceiling effect dose of palonosetron [27]. Since then, however, the efficacy of higher doses has not been evaluated in most studies [25]. Based on the results of the present study, further clinical research might be needed to verify the value of the current fixed dose (0.075 mg) for PONV in comparison with higher doses.

In conclusion, a three-compartment model described the pharmacokinetics of palonosetron well, and the pharmacokinetic parameters of palonosetron were affected by body size, especially by LBW. From our simulation results, LBW-based dosing might be suitable for high-weight patients to avoid possible underdosing; nevertheless, the current fixed dosing is still acceptable for most adult patients with normal weight due to low pharmacokinetic variability.

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Compliance with ethical standards

Conflict of interest No external funding and no competing interests declared.

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