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ORIGINAL PAPER

Population pharmacokinetics of ramosetron

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Abstract Ramosetron is a selective serotonergic 5-hydroxy-tryptamine receptor 3 antagonist that is used to prevent and treat postoperative nausea and vomiting. This study aimed to characterize the population pharmacokinetics of ramosetron in patients undergoing surgery with general anesthesia. Patients aged 19–80 years received a single intravenous bolus of ramosetron (0.3, 0.45, or 0.6 mg) 30 min before the end of surgery. Blood samples were collected, and plasma concentrations of ramosetron were measured by high performance liquid chromatography-tandem mass spectrometry. Pooled data from 50 patients and 479 pharmacokinetic samples were used for population pharmacokinetic analysis using the nonlinear mixed effect modeling program (NONMEM®). The pharmacokinetics of ramosetron was best described by a three-compartment mammillary model with first-order elimination. Based on allometric principles, body weight was incorporated in the base model, along with fixed allometric exponents. The typical value of clearance was 0.19 L/h in a 60-kg subject, and it decreased approximately 3 % for every year of age, starting at age of 57. The bootstrap method and visual predictive check showed that the final pharmacokinetic model was appropriate. A population pharmacokinetic model of ramosetron was constructed in adult surgical patients, providing a foundation for further defining the relationship between ramosetron dose and postoperative nausea and vomiting.

Keywords Population pharmacokinetics · Postoperative nausea and vomiting · NONMEM · Ramosetron · Serotonin 5-HT3 receptor antagonist

Introduction

Postoperative nausea and vomiting (PONV) are distressing and are frequent events after anesthesia. PONV is associated not only with patient dissatisfaction, but also with dehydration, electrolyte imbalance, and disruption of surgical repair [1]. The general incidence of vomiting is about 30 %, and the incidence of nausea is about 50 %; however, the PONV rate can be as high as 80 % in high-risk patients [2, 3]. Among several pharmacologic agents, 5-hydroxy-tryptamine receptor 3 (5-HT_3) antagonists are predominantly used as a first-line treatment for PONV, due to their efficacy and safety [4, 5].

Many studies have evaluated the antiemetic effect of 5-HT_3 antagonists [6–10]. However, in clinical practice, some patients still suffer from acute and delayed onset PONV, despite prophylactic use of 5-HT_3 antagonists. In addition, various background factors (e.g., individual, anesthetic, and surgical risk factors of PONV) are associated with PONV [11]. Moreover, a variety of factors are known to influence the disposition of 5-HT_3 antagonists in humans, including body size, age, sex and hepatic function [12, 13]. Nevertheless, the current dosing guidance for 5-HT_3 antagonists do not account for

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Table 1 Summary of categorical and continuous demographic data

Characteristic	Ramosetron			Total
	0.3 mg	0.45 mg	0.6 mg	
Number of patients (male/female)	17 (5/12)	17 (4/13)	16 (6/10)	50 (15/35)
Age (year)	60 [42.0–74]	58 [35–79]	69.5 [24–77]	60 [24–79]
Weight (kg)	60.0 [44.0–73.0]	54.0 [43.0–75.0]	62.5 [48–83]	58.5 [43.0–83.0]
Height (cm)	160 [151–170]	156 [145–169]	160 [150–175]	158 [145–175]
Ideal body weight[a] (kg)	56.9 [44.2–65.0]	48.8 [38.8–65.0]	53.3 [43.3–70.5]	51.1 [38.8–70.5]
Lean body mass[b] (kg)	44.2 [35.2–55.0]	40.4 [33.0–57.0]	43.7 [36.2–59.0]	43.4 [33.0–59.0]
Body mass index (kg/m^2)	22.9 [18.0–28.1]	21.6 [18.9–27.2]	24.7 [19.1–30.5]	23.0 [18.0–30.5]

Values are the median [minimum to maximum]

[a] Calculated by the Devine formula

[b] Calculated by the James formula

patient characteristics or PONV risk factors, resulting in prophylactic failure [14].

Ramosetron (Nasea®; Astellas, Tokyo, Japan), a new generation 5-HT$_3$ antagonist developed recently in Japan, has a higher potency and longer-lasting antiemetic action than first-generation 5-HT$_3$ antagonists such as ondansetron [13, 15]. Ramosetron is known to undergo extensive hepatic oxidative metabolism mediated through multiple cytochrome P450 forms, mainly CYP1A2 and CYP2D6 [16], which are similar to other 5-HT$_3$ antagonists [17, 18]. Although several population pharmacokinetic (PK) analyses of ondansetron have been conducted in adults and pediatric patients [19–21], no reports have evaluated ramosetron. This may be because ramosetron has only been approved for the prevention of nausea and vomiting in Japan, Korea, and other Southeast Asian countries [22].

Population PK analysis is a useful and valid approach to quantify drug exposure-clinical response relationships, and it may lead to dosage modification based on the patient characteristics that influence PK parameters. This study aimed to develop a population PK model of ramosetron and to identify the impacts of patient characteristics on ramosetron PK variability using non-linear mixed effects modeling.

Materials and methods

Study design

The study was designed as a double-blind, randomized, clinical trial. Patients aged 19–80 years with American Society of Anesthesiologists physical status I or II, who were scheduled to undergo elective surgery under general anesthesia, were studied. Patients who had received selective serotonin reuptake inhibitors or who had any abnormal organ function were excluded.

All patients fasted from midnight to the time of surgery and received no premedication. Upon arrival in the operating room, a 20-gauge catheter was placed into the radial artery to monitor blood pressure and to take blood samples. Routine monitoring included noninvasive measurement of blood pressure, heart rate, electrocardiography, and pulse oximetry. Anesthesia was induced with propofol, and maintained with sevoflurane and remifentanil. All patients were transferred to the post-anesthesia care unit after surgery, and transferred to the ward when they were fully awake.

Patients were randomly allocated into one of three ramosetron groups (0.3, 0.45, and 0.6 mg) according to computer-generated random table. Personnel not involved in the study prepared identical syringes containing the drugs diluted in 10 mL, and all other study personnel and patients were blinded to treatment assignment. About 30 min before the end of surgery, the investigational drugs were given intravenously. Arterial blood samples (5 mL) were drawn at preset intervals: immediately before drug administration, 2, 5, 10, 15, and 30 min, and 1, 2, 6, 24, and 48 h after an IV bolus injection of ramosetron.

The study was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (Hwasun, Republic of Korea) and conducted according to the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients before the start of the study.

Measurement of ramosetron concentrations

The samples for the ramosetron assay were collected into tubes containing ethylenediaminetetraacetic acid-Na and immediately centrifuged at 1500×*g* for 10 min at 4 °C. The plasma was then stored at −70 °C until use. Plasma concentrations of ramosetron were analyzed using validated high performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS). In brief, 200 µL of plasma sample was mixed with 20 µL of internal standard (5 ng/mL of risperidone). Then, 1.5 mL tert-butyl methyl ether was added, and the mixture was vortexed for 2 min and centrifuged at 12,000 rpm for 2 min. The supernatants were transferred and evaporated under nitrogen. The residue was reconstituted in 100 µL of 40 % acetonitrile, and a volume of 10 µL was injected into the HPLC–MS/MS system [HPLC system: Shimadzu LC-20A HPLC system (Shimadzu Co., Kyoto, Japan); MS/MS system: API 4000Q-TRAP mass spectrometer (AB SCIEX, Framingham, MA, USA)]. A Gemini C18 2.0 × 100 mm (Phenomenex, Torrance, CA, USA) column was used; the mobile phase consisted of ammonium acetate (10 mM): acetonitrile (40:60, v/v). The flow rate was maintained at 0.25 mL/min.

The lower limit of ramosetron quantification was 0.1 ng/mL. Linear calibration curves were validated in the ranges of 0.1–100 ng/mL ($r^2 = 0.98$). Precision and accuracy of intra- and inter-day measures were verified within 15 % and 85–115 %, respectively.

Population pharmacokinetic modeling

Population non-linear mixed effect modeling was performed with NONMEM® software (version 7.3; Icon Developmental Solutions, Ellicott City, USA) with the PREDPP subroutine ADVAN 6. The Beal M3 method [23] was implemented to consider concentrations below the quantification limit, and the Laplacian estimation method with the interaction option was used.

Selection of the structural model

One-, two-, and three-compartment mammillary models with first-order elimination were evaluated for fitness to ramosetron plasma concentration data. As for the residual variability, additive, proportional and combined forms were tested. Inter-individual variability (IIV) was assumed to be log normally distributed and was added to all PK parameters. The exclusion of IIV terms on PK parameters was tested one by one with an assessment of the overall fit of a model.

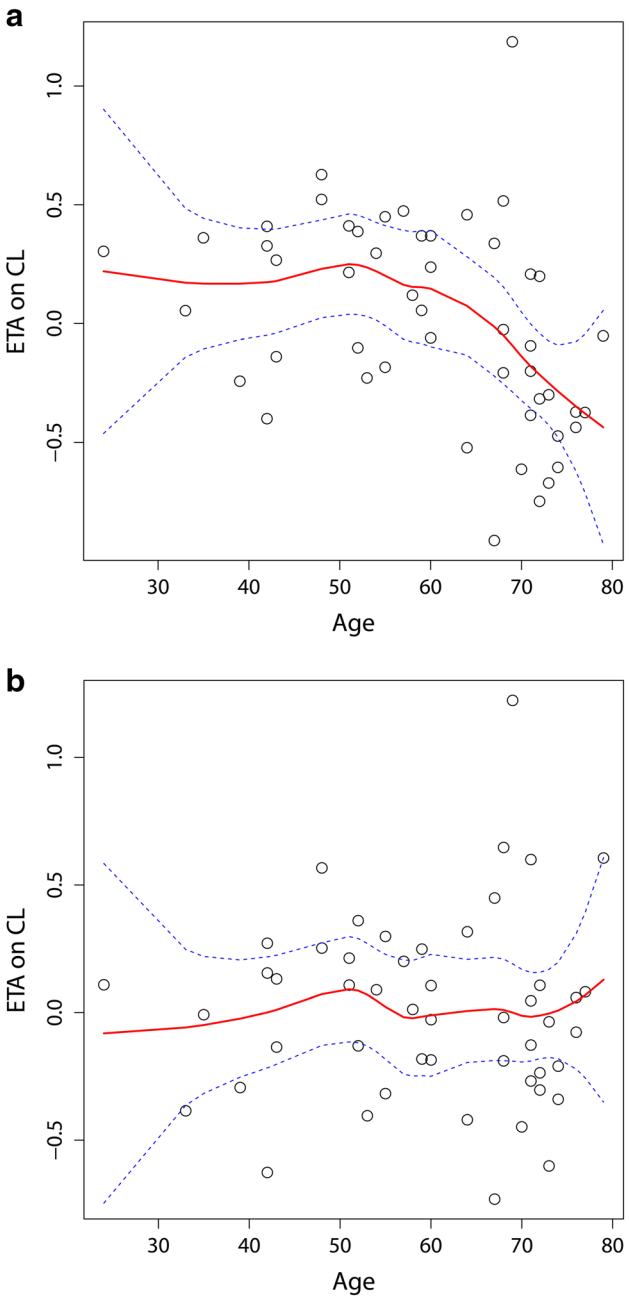


Fig. 1 ETA covariate plots on clearance (CL) versus age for the base model (**a**) and final model (**b**). *Solid* and *dashed lines* represent LOWESS regression line and 95 % confidence interval

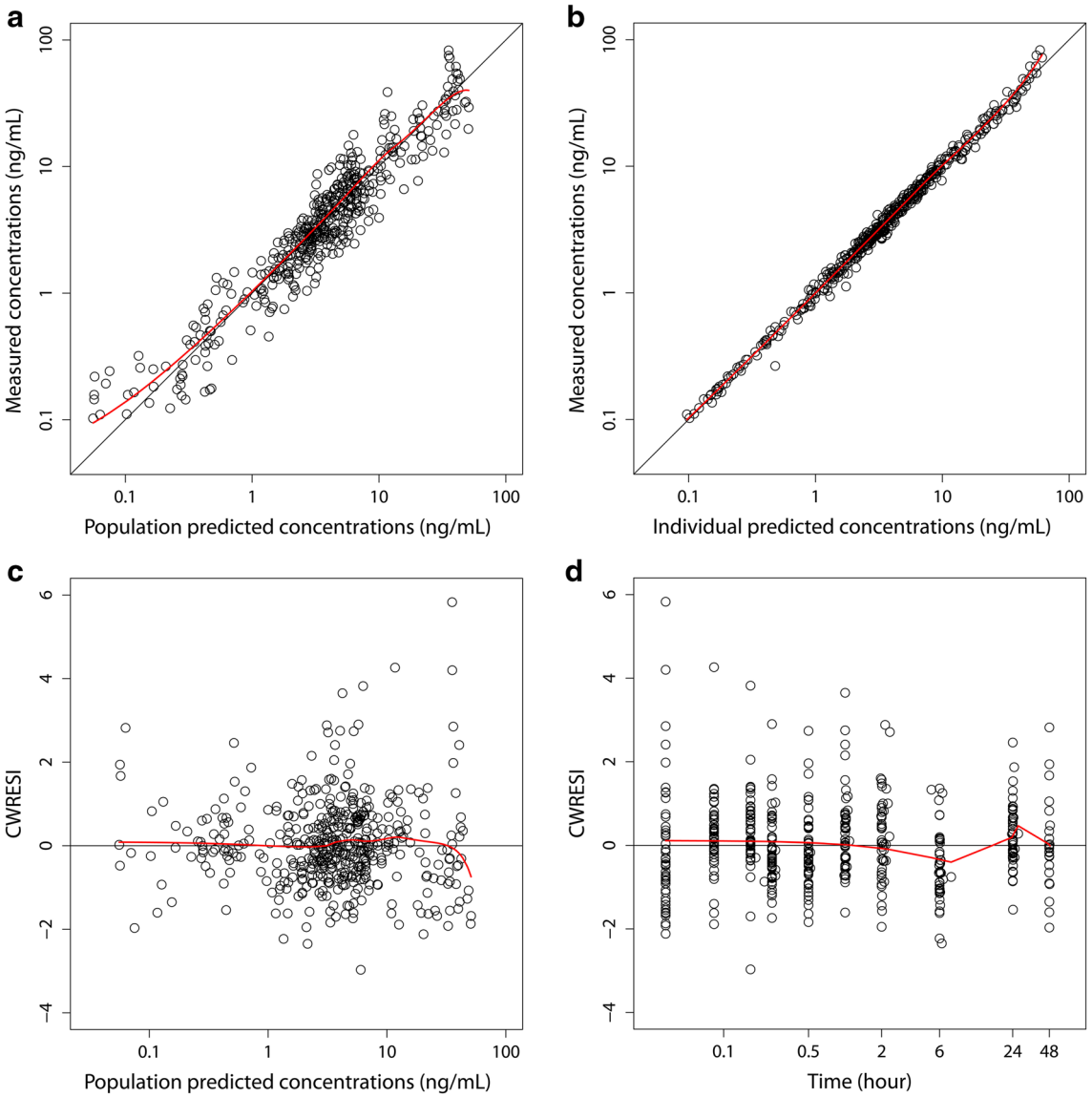


Fig. 2 Goodness-of-fit plots of the final model for ramosetron. The population and individual predictions were distributed around the line of identity (*black solid line*). The conditional weighted residuals with interaction (CWRESI) were generally distributed around the zero line (versus population predicted concentrations or time)

Covariate inclusion

Initially, based on the allometric principles, body weight was introduced together with all PK parameters. Fixed allometric exponents of 0.75 and 1 were used for all clearance and volume parameters of ramosetron, respectively. Ideal body weight (IBW) [24] or lean body mass (LBM) [25] was also tested in place of body weight for each PK parameter one by one. After an allometric scaling model was established, the influence of all potential covariates such as body weight, height, IBW, LBM and body mass index (BMI), age, and sex was assessed with various forms of covariate models including linear, power, exponential, and hockey-stick functions. For continuous covariates, the effects were centered with the median value of the population. Covariate model building was accomplished by a mixed stepwise forward inclusion and backward elimination, based on change in OFV. The

Table 2 Population pharmacokinetic parameter estimates, inter-individual variability (CV %), and median parameter values with confidence interval (CI) of the nonparametric bootstrap (BS) replicates of the final pharmacokinetic model of ramosetron

Model equation	
$V_1 = \theta_{V1} \times (WT/60)$	Age $\geq \theta^{INF}$
$V_2 = \theta_{V2} \times (WT/60)$	$CL = \theta_{CL} \times (WT/60)^{0.75} \times e^{-\theta AGE \times (AGE - \theta INF)} \times e^{\eta CL}$
$V_3 = \theta_{V3} \times (WT/60) \times e^{\eta V3}$	Age $< \theta^{INF}$
$Q_1 = \theta_{Q1} \times (WT/60)^{0.75} \times e^{\eta Q1}$	$CL = \theta_{CL} \times (WT/60)^{0.75} \times e^{\eta CL}$
$Q_2 = \theta_{Q2} \times (WT/60)^{0.75} \times e^{\eta Q2}$	

Parameter	Estimate (% RSE)	BS median	BS 95 % CI
V_1 (θ_{V1}, L)	4.95 (6.57)	4.90	4.33–5.71
V_2 (θ_{V2}, L)	31.9 (4.98)	31.4	22.3–36.2
V_3 (θ_{V3}, L)	88.3 (8.13)	89.5	76.7–104.0
Cl (θ_{CL}, L/h)	0.190 (6.42)	0.189	0.156–0.217
Q_1 (θ_{Q1}, L/h)	1.69 (10.0)	1.67	1.36–1.97
Q_2 (θ_{Q1}, L/h)	0.895 (5.34)	0.931	0.708–1.180
θ^{AGE}	0.029 (25.4)	0.036	0.016–0.135
θ^{INF} (age)	57 (3.07)	60	48–69
IIV for V_3 (%CV)	56.7	0.286	0.136–0.566
IIV for Cl (%CV)	38.1	0.142	0.068–0.229
IIV for Q_1 (%CV)	32.2	0.094	0.047–0.159
IIV for Q_2 (%CV)	59.2	0.340	0.176–0.610
Proportional residual error (%CV)	12.3	0.124	0.110–0.135

Of the 2000 bootstrap runs, 1712 converged, giving a convergence rate of 85.6 %. CIs were determined from the results from all replicates. The eta-shrinkage values for V_3, Cl, Q_1, and Q_2 were 2.2, 3.9, 9.4, and 3.1 %, respectively

WT, body weight; θ^{AGE}, approximate %change in CL per year; θ^{INF}, a clearance inflection point for age; V_1, V_2, and V_3, volume of central compartment, peripheral compartment 2, and peripheral compartment 3; CL, clearance; Q_1 and Q_2, inter-compartmental clearance between compartments 1 and 2, and between compartments 1 and 3; %RSE, percent relative standard error; IIV, inter-individual variability

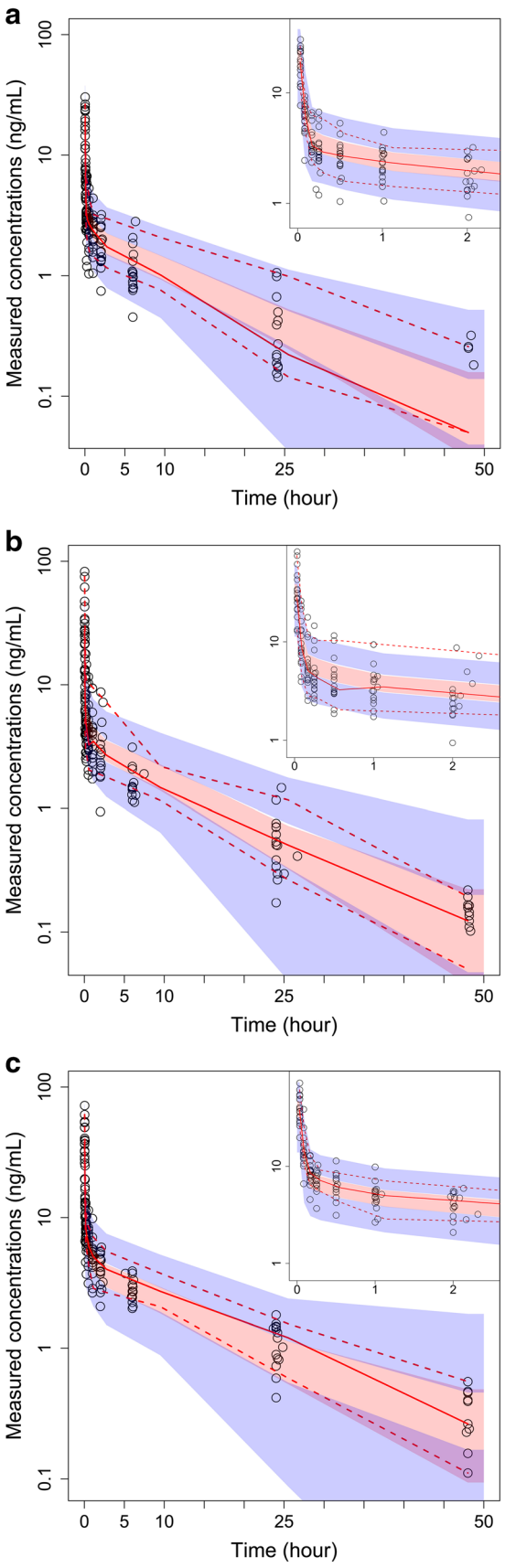
significance level for the forward inclusion step and backward elimination were 0.05 (OFV drop >3.84 for one degree of freedom and 5.99 for two degrees of freedom) and 0.005 (OFV drop >7.88 for one degree of freedom and 10.60 for two degrees of freedom), respectively.

Model evaluation

The goodness of fit of the model was evaluated graphically using plots of predicted versus observed data, random effect analysis, and visual predictive checks (VPCs), which were facilitated by Xpose (version 4.3.2) and PsN (Pearl-speaks-NONMEM, version 4.2.0), as described earlier [26–30]. The 95 % confidence intervals (CIs) for mean population PK parameters were determined by a nonparametric bootstrap analysis [31] using fit4NM (version 3.5.1, Eun-Kyung Lee and Gyu-Jeong Noh, Seoul, Republic of Korea; www.fit4nm.org). A total of 2000 bootstrap replicates were generated by random sampling from the original data set with replacement, and the parameters were estimated using the final population PK model.

Results

Of the 54 patients screened for enrollment, 51 were enrolled in the randomized clinical trial. One patient randomized to the 0.6 mg group was withdrawn from the study due to protocol violation before investigational drug injection. Consequently, 50 patients (15 males and 35 females) received ramosetron and gave blood samples. The main demographics and baseline characteristics of all evaluated patients did not differ among the three groups (Table 1). No hepatic or renal dysfunction was found in the



◀**Fig. 3** Visual predictive checks of ramosetron in plasma based on 2000 datasets with bolus injection of 0.3 mg (**a**), 0.45 mg (**b**) and 0.6 mg (**c**). *Solid* and *dashed lines* are 5th, 50th and 95th percentiles of the observation. The shaded areas represent the 95 % confidence interval for each percentile of the simulation. The observed concentrations are also plotted as *open circles*

patients' histories. The final pooled data set for population PK analysis consisted of 479 samples (3.5 % were below the lower limit of quantification of 0.1 ng/mL).

The structural model

A three-compartment model with first-order elimination was selected because it fit the data better than the one-compartment and two-compartment models. Primary PK parameters included the volume of compartment 1 (V1), 2 (V2), and 3 (V3), and clearance (CL), both inter-compartmental clearance between compartments 1 and 2 (Q1), and between 1 and 3 (Q2). When using the combined error model, the estimate of the additive component was small and could be removed from the model without affecting the fit. The proportional error model was better for modeling residual variability compared with additional error. Therefore, the three-compartment model with proportional error was selected as a base model.

Covariate inclusion

Body weight was included a priori as a fixed covariate with an allometric exponent of 0.75 for clearance parameters and 1 for volume parameters in the base model; there are several reports that support theoretically [32, 33] and empirically [34, 35] fixing the allometric exponent. This allometric scaling by body weight resulted in an OFV reduction of 13.8 and improved model fit. For other size descriptors including, IBW and LBM, there was no improvement in OFV or model fit compared with the allometric model using body weight.

In the forward inclusion process, covariates were univariately added to the initial allometric model using body weight. Age on CL with a hockey-stick function was incorporated into the model with an 11.3 reduction in the OFV and a 7 % reduction in IIV for CL. In this model, CL was constant before age of 57, but decreased in those older than 57. ETA covariate plots of CL versus age for the base and final model are shown in Fig. 1. After inclusion of age on CL, any other significant covariate including sex was not found on all PK parameters. Stepwise backward elimination did not result in removal of age on CL.

Model evaluation

The basic goodness-of-fit plots of the final population PK model are shown in Fig. 2. The diagnostic plots showed that the individual predicted values were consistent with the observed values and that the conditional weighted residuals with interaction (CWRESI) were generally distributed around zero and did not reflect any systematic deviations. Population PK parameter estimates of the final model and the results of the nonparametric bootstrap replicates for ramosetron are summarized in Table 2. The results of the visual predictive check showing the 5th, 50th (median), and 95th percentile ramosetron concentrations based on 2000 data sets for each dose group are shown in Fig. 3. The results of the bootstrap and VPC analysis confirmed the predictive ability, model stability, and precision of the parameter estimates.

Discussion

The aim of this study was to estimate ramosetron PK parameters and to identify the clinical determinants of ramosetron PK variability. Population analysis demonstrated that the plasma concentration of ramosetron was best described using a three-compartment mammillary model with body weight and age. To our knowledge, this is the first study for the population PK analysis of ramosetron.

The effect of body weight with an allometric model was included in the population model. However despite reducing the OFV, the inclusion of body weight decreased IIV for all PK parameters by less than 5 %, suggesting that a considerable portion of the variability was not explained by body weight.

The effect of age on ramosetron clearance was identified as the most statistically significant covariate in the present study. The typical value of clearance was 0.19 L/h in a 60-kg subject, and clearance decreased by approximately 3 % for every year of age, starting at age 57. Clearance was estimated to be 50 % lower in an 81-year old patient relative to a 57-year old patient. A significant decrease in clearance by metabolism of ramosetron may be attributed to a reduction in hepatic function with age [36].

Previous studies have shown a sex difference in the pharmacokinetics of 5-HT_3 antagonists, including ramosetron, ondansetron, and alosetron [37–39], which are metabolized by CYP1A2 [16, 39, 40]. This may be accounted for by sex-related differences in CYP1A2-mediated activity [41]. However, sex was not a significant covariate in this study. The discrepancy between previous studies and this study cannot be readily explained. Kadokura et al. [16] observed that the increase in $AUC_{0\text{-inf}}$ was more pronounced than the increase in $t½$ after oral administration of ramosetron, although both parameters increased. They speculated that inhibition of CYP1A2 affects not only elimination but also the first pass effect, resulting in a higher bioavailability of ramosetron in female subjects. It is likely that the route of administration of ramosetron, that is, intravenous rather than oral, is, at least in part, responsible for the discrepancy between the studies. In fact, Koch et al. [12] demonstrated a two-fold larger sex difference in serum concentrations of alosetron after oral dosing compared with intravenous dosing in elderly subjects, suggesting the importance of the first-pass component of metabolic clearance in achieving of high concentrations of alosetron.

Trials to study PONV with the use of the 5-HT3 receptor antagonists are expensive and challenging to design and manage [17]. Thus, it is hard to determine the least effective dose once an effective dose with acceptable safety has been established. Population PK analysis is an important tool to solve these problems, because optimal dosage regimens can be selected through model-based simulation. The results of this present population PK analysis of ramosetron allow for the characterization of ramosetron exposure in individual patients based on their body weight and age, and provide framework from which the necessity, manner, and performance of potential dosing modifications can be explored.

Conclusions

A population PK model of ramosetron that adequately described the differences in ramosetron pharmacokinetics with body weight and age was developed. The final model was found to be appropriate using a bootstrap method and VPCs. The population PK analysis of ramosetron presented herein provides a foundation for further defining the relationship between ramosetron dose and PONV in surgical patients.

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Appendix

NONMEM code for the final pharmacokinetic model of intravenous ramosetron

```
$PROB 101; three compartment with proportional error model (Beal M3)
$DATA NaseaPK_BLQ.csv IGNORE=#
$INPUT ID TIME AMT RATE DV MDV TYPE AGE WT HT GROUP SEX LBM IBW BMI
$SUBROUTINE ADVAN6 TOL=9
$MODEL COMP(CENTRAL,DEFDOSE) COMP(Periph1) COMP(Periph2)
$PK
  TH1 = THETA(1) ;V1
  TH2 = THETA(2) ;V2
  TH3 = THETA(3) ;V3
  TH4 = THETA(4) ;CL
  TH5 = THETA(5) ;Q1
  TH6 = THETA(6) ;Q2
  TH7 = THETA(7) ;Prop
  TH8 = THETA(8) ;Age inflection point
  TH9 = THETA(9) ;Age effect on CL
  AGEINF = TH8

  TVV1 = TH1 * (WT/60)**1
  TVV2 = TH2 * (WT/60)**1
  TVV3 = TH3 * (WT/60)**1
  IF (AGE.GE.AGEINF) THEN
  TVCL = TH4 * (WT/60)**0.75 * EXP(TH9 * (AGE-AGEINF))
  ELSE
  TVCL = TH4 * (WT/60)**0.75
  ENDIF
  TVQ1 = TH5 * (WT/60)**0.75
  TVQ2 = TH6 * (WT/60)**0.75
```

```
   MU1 = LOG(TVV1)
   V1 = EXP(MU1 + ETA(1))
   MU2 = LOG(TVV2)
   V2 = EXP(MU2 + ETA(2))
   MU3 = LOG(TVV3)
   V3 = EXP(MU3 + ETA(3))
   MU4 = LOG(TVCL)
   CL = EXP(MU4 + ETA(4))
   MU5 = LOG(TVQ1)
   Q1 = EXP(MU5 + ETA(5))
   MU6 = LOG(TVQ2)
   Q2 = EXP(MU6 + ETA(6))

   K10=CL/V1
   K12=Q1/V1
   K13=Q2/V1
   K21=Q1/V2
   K31=Q2/V3

$DES
   DADT(1) = A(2)*K21+A(3)*K31-A(1)*(K10+K12+K13)
   DADT(2) = A(1)*K12-A(2)*K21
   DADT(3) = A(1)*K13-A(3)*K31

$ERROR
   IPRED = F
   LOQ = 0.1
   W = SQRT(0.00001 + TH7**2 * F*F)
   IF (TYPE.EQ.1) THEN
      F_FLAG = 0
      IRES = DV - IPRED
      IWRES = IRES / W
      Y = IPRED + W*EPS(1)
   ENDIF
   IF (TYPE.EQ.2) THEN
      F_FLAG = 1
      DUM = (LOQ-IPRED)/W
      CUMD = PHI(DUM)
      Y = CUMD
      MDVRES = 1
   ENDIF

$THETA
   (0, 5)
   (0, 30)
   (0, 90)
   (0, 0.2)
   (0, 2)
   (0, 1)
   (0, 0.1)
   (0, 55)
   0.02

$OMEGA
   0 FIX
   0 FIX
   0.3
   0.2
```

```
  0.1

  0.3


$SIGMA

  1 FIX


$ESTIMATION MAX=9999 PRINT=5 METHOD=1 INTER LAPLACIAN NUMERICAL SLOW NOABORT
MSFO=101.MSF
$COVARIANCE PRINT=E


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