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ORIGINAL ARTICLE

Population pharmacokinetics of aprepitant and dexamethasone in the prevention of chemotherapy-induced nausea and vomiting

Susumu Nakade · Tomoya Ohno · Junsaku Kitagawa · Yoshitaka Hashimoto · Masahiro Katayama · Hiroshi Awata · Yasuo Kodama · Yasuyuki Miyata

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Abstract
Purpose To develop a population pharmacokinetic model of aprepitant and dexamethasone in Japanese patients with cancer, explore the factors that affect the pharmacokinetics of aprepitant, and evaluate the effect of aprepitant on the clearance of intravenous dexamethasone.
Methods A total of 897 aprepitant concentration measurements were obtained from 290 cancer patients and 25 healthy volunteers. For dexamethasone, a total of 847 measurements were obtained from 440 patients who were co-administered aprepitant (40, 125 mg, or placebo). Plasma concentration of aprepitant and dexamethasone were determined by liquid chromatography connected with a tandem mass spectrometer and analyzed by a population approach using NONMEM software.
Results The plasma concentration time course of aprepitant was described using a one-compartment model with first-order absorption and lag time. Oral clearance (CL/*F*) of aprepitant was changed by aprepitant dose at doses of 40 or 125 mg. Body weight was the most influential intrinsic factor to CL/*F* of aprepitant. Age, ALT, and BUN also had mild effects on the CL/*F*. Typical population estimates of CL/*F*, apparent distribution volume (V_d/F), absorption constant (K_a) and absorption lag time were 1.54 L/h, 72.1 L, 0.893/h and 0.295 h, respectively. Inter-individual variability in CL/*F*, V_d/F and K_a were 53.9, 21.0, and 141%, respectively; intra-individual variability was 27.7%. The plasma concentration time course of intravenous dexamethasone was also described using a one-compartment model. Clearance of dexamethasone was decreased 24.7 and 47.5% by co-administration of aprepitant 40 and 125 mg. All final model estimates of aprepitant and dexamethasone fell within 10% of the bootstrapped mean.
Conclusions A pharmacokinetic model for aprepitant has been developed that incorporates body weight, age, ALT, BUN and aprepitant dose to predict the CL/*F*. The results of population pharmacokinetic analysis of dexamethasone support dose adjustment of dexamethasone in the case of co-administration with aprepitant.

Keywords Aprepitant · Chemotherapy-induced nausea and vomiting · Dexamethasone · Population pharmacokinetics

Abbreviations

ALB	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CINV	Cancer chemotherapy-induced nausea and vomiting
CL	Clearance
CL/*F*	Oral clearance
CYP	Cytochrome P450
K_a	Absorption rate constant
OBJ	Objective function

S. Nakade (✉) · T. Ohno · J. Kitagawa · Y. Hashimoto · Y. Miyata
Pharmacokinetic Research Laboratories, Ono Pharmaceutical Co., Ltd, 17-2 Wadai, Tsukuba, Ibaraki 300-4247, Japan
e-mail: s.nakade@ono.co.jp

M. Katayama · H. Awata
Development Planning, Ono Pharmaceutical Co., Ltd, Osaka, Japan

Y. Kodama
Laboratory of Bio-Pharmaceutics, Faculty of Pharmaceutical Sciences, Josai International University, Togane, Chiba, Japan

t_{lag} Absorption lag time
V_d Distribution volume
V_d/F Apparent distribution volume

Introduction

One of the most common adverse effects of cytotoxic agents is nausea and vomiting, both of which have a considerable negative impact on the quality of life of cancer patients. Aprepitant (Emend®), an orally available, selective neurokinin-1 (NK-1) receptor antagonist, has recently been approved in the USA and Europe for the treatment of moderately and highly emetogenic chemotherapy. Aprepitant is effective for both acute and delayed chemotherapy-induced nausea and vomiting (CINV), and is used in combination with a 5-hydroxytryptamine-3 (5HT3) antagonist (e.g., ondansetron) and a corticosteroid (e.g., dexamethasone) [1, 21]. In randomized placebo-controlled clinical trials, the addition of aprepitant to ondansetron and dexamethasone significantly improved protection against emesis [5, 8, 20]. The recommended dose-regimen of aprepitant is 125 mg prior to chemotherapy on day 1 and 80 mg on days 2 and 3 [1, 21]. The recommended dose regimen has not been decided in Japan, however, because of under-testing.

The absolute bioavailability of a single oral dose of the aprepitant 125 mg capsule is approximately 60%. Peak plasma concentrations occur approximately 4 h after administration, and the half-life is approximately 11 h [17]. Oral administration of the capsule with a standard breakfast has no clinically meaningful effect on bioavailability. Aprepitant is eliminated primarily by metabolism and is not renally excreted. In vitro studies indicate that aprepitant is primarily metabolized by CYP3A4 [10, 14].

The typical pharmacokinetic profile of aprepitant in healthy subjects is as noted above. However, population pharmacokinetics of Japanese cancer patients has not been reported. This study was aimed to develop a population pharmacokinetic model of aprepitant using plasma concentrations on two Phase I and one Phase II pivotal studies in Japan, and also to explore the factors that affect aprepritant pharmacokinetics and inter- and intra-individual variability in cancer patients.

The recommended dose regimen of aprepitant (125 mg) results in moderate inhibition of cytochrome P4503A4 (CYP3A4)[16, 25]. Dexamethasone, which is co-administered with aprepitant for the prevention of CINV, is metabolized by CYP3A4 [12, 19]. It has been reported that the AUC of dexamethasone was increased to approximately 2.2-fold when aprepitant at a dose of 125 mg and oral dexamethasone were co-administered [19]. In a Phase II study, intravenous dexamethasone, used more frequently than oral dexamethasone in Japan, was co-administered with aprepitant. However, the effect of aprepitant on the pharmacokinetics of intravenous dexamethasone has not been reported. Therefore, this study also aimed to evaluate that the effect of aprepitant on the clearance of intravenous dexamethasone.

Materials and methods

Subjects/patients and trial designs

Aprepitant data was obtained from 25 healthy volunteers in two Phase I studies (single and multiple dose studies) and 290 cancer patients in a Phase II pivotal study. Dexamethasone data was also obtained from 440 cancer patients in the Phase II study (Table 1). All of these studies were performed during the clinical testing of aprepitant in Japan between March 2001 and January 2006. The study protocols were reviewed and approved by the institutional review boards of each clinical study site. Written informed consent was obtained from each subject or patient.

Studies 1 and 2 were Phase I trials performed in healthy male volunteers. In Study 1, subjects were administered a

Table 1 Sources of plasma aprepitant and dexamethasone concentration data

Study number	Study objective	Dose (mg)	Number of subjects	Number of measurements	Average number of measurements
Aprepitant					
1	Phase I trial, single dose	125	7	102	14.6/subject
2	Phase I trial, single dose	40, 80	18	238	13.2/subject
3	Phase II trial	40, 125	290	557	1.9/patient
	Total		315	897	
Dexamethasone					
3	Phase II trial	12 (placebo)[a], 8 (40)[a], 6 (125)[a]	440	847	1.9/patient

[a] Aprepitant dose on day 1 is represented in parentheses

Table 2 Dose-regimen for the prevention of chemotherapy-induced nausea and vomiting in a Phase II trial

Treatment	Medication	Day 1	Day 2–3	Day 4–5
Placebo	Aprepitant (po)	Placebo	Placebo	Placebo
	Dexamethasone (iv)[a]	8 mg	12 mg	–
	Granisetron (iv)	40 μg/kg	–	–
Low dose (40/25 mg)	Aprepitant (po)	40 mg	25 mg	25 mg
	Dexamethasone (iv)[a]	6 mg	8 mg	–
	Granisetron (iv)	40 μg/kg	–	–
High dose (125/80 mg)	Aprepitant (po)	125 mg	80 mg	80 mg
	Dexamethasone (iv)[a]	4 mg	6 mg	–
	Granisetron (iv)	40 μg/kg	–	–

[a] Dexamethasone dose was adjusted to give same exposure level of dexamethasone between 3 treatments considering drug-drug interaction of aprepitant.

single dose of 125 mg of aprepitant. One hundred two blood samples were drawn from the vein of each subject for measuring aprepitant concentrations in plasma at 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, 72, and 96 h after administration. Study 2 had 2 components, single and multiple dosing parts. The data of single dosing part at the dose of 40 and 80 mg aprepitant was used for the analysis. Two hundred and thirty eight plasma samples were collected at the same sampling times on Study 1.

Study 3 was a Phase II trial performed in 453 cancer patients. Patients who had histologically confirmed solid tumors and who were scheduled to receive their first cisplatin (at a dose of at least $\geq$70 mg/m^2) were enrolled. Patients with any of the following conditions were excluded: abnormal laboratory values [including white blood count (WBC)] $< 3.0 \times 10^9$ cells/L and absolute neutrophil count $< 1.5 \times 10^9$ cells/L, platelet count $< 100 \times 10^9$/L, aspartate aminotransferase (AST) $>$ 2.5 N (normal value), alanine aminotransferase (ALT) $>$ 2.5 N, bilirubin $>$ 1.5 N or creatinine $>$ 1.5 N). Other exclusion criteria were with the same as in previous studies [9, 8, 13].

Each anti-emetic treatment consisted of a 5-day regimen of either oral aprepitant or placebo, plus a standard therapy regimen as shown in Table 2. Patients in the standard therapy group received intravenous granisetron (40 μg/kg) and intravenous dexamethasone (12 mg) on day 1, followed by intravenous dexamethasone (8 mg) once daily on days 2 and 3. Patients in the low dose (40/25-mg) aprepitant therapy group received oral aprepitant (40 mg) plus intravenous granisetron (40 μg/kg) and intravenous dexamethasone (6 mg) on day 1, oral aprepitant (25 mg) once daily on days 2 through 5 and intravenous dexamethasone (8 mg) once daily on days 2 and 3. Patients in the high dose (125/80 mg) aprepitant therapy group received oral aprepitant (125 mg) plus intravenous granisetron (40 μg/kg) and intravenous dexamethasone (6 mg) on day 1, oral aprepitant (80 mg) once daily on days 2 through 5 and intravenous dexamethasone (4 mg) once daily on days 2 and 3.

Blood sampling for aprepitant was conducted at two time points 7–11 h after the starting of chemical therapy on day 1, and before administration of aprepitant on day 2. The blood sampling for dexamethasone was also conducted at two time points (3–5 and 7–11 h after the beginning of drug therapy on day 1).

Plasma concentration of aprepitant and dexamethasone

Plasma concentrations of aprepitant were determined by liquid chromatography connected with a tandem mass spectrometer (LC/MS/MS) [7]. Plasma samples (0.1 mL) containing the internal standard were extracted with methyl *t*-butyl ether under basic conditions. The dried extract was reconstituted in the mobile phase and an aliquot was injected onto the LC/MS/MS for quantification. The quantitative ranges of analytes in plasma were 1–2,000 ng/mL. All of the precision values for analysis (CV%) of quality control samples (three concentrations samples) were within 15%.

Plasma concentrations of dexamethasone were also determined by LC/MS/MS. Plasma samples (0.25 mL) containing the internal standard were extracted with diethyl ether under basic conditions. The dried extract was reconstituted in methanol/water (7:3) and an aliquot was injected onto the LC/MS/MS. The quantitative ranges of analytes in plasma were 0.25–100 ng/mL. All of the precision values for analysis (CV%) of quality control samples (three concentrations samples) were within 15%.

Population pharmacokinetic model of aprepitant and dexamethasone

The population pharmacokinetic model was developed using the nonlinear mixed-effect modeling software NONMEM (Ver.V level 1.1) [2]. The first order method was used for parameter estimation. After investigation of one- and two-compartment models, we found that the concentration time course of aprepitant was well described by a one-compartment model. The model parameters were the absorption rate (K_a), absorption lag time (t_{lag}), apparent distribution volume (V_d/F), and oral clearance (CL/F). The

pharmacokinetic profile of dexamethasone after intravenous administration was described using a one-compartment model. Here, the model parameters were the distribution volume (V_d), and the total body clearance (CL). The inter-individual and intra-individual variability in pharmacokinetic parameters of both drugs were investigated using additive and proportional error models. The inter-occasion variability was not investigated because the pharmacokinetic sampling was performed only after the first dose of each drug in each of the three studies.

Starting from a simple one-compartment model, a variety of covariates that could influence the pharmacokinetics of aprepitant or dexamethasone were added stepwise to the basic model (forward selection method). An individual covariate was considered to improve the model significantly if the difference in an objective function value (ΔOBJ) between the basic model and tested model was greater than 3.84 ($P < 0.05$). Covariates considered for inclusion in the model were subject demographic factors (gender, body weight, age), laboratory values (routine hematology and blood chemistry), aprepitant dose, and smoking history. The difference between healthy volunteers and patients was also evaluated for aprepitant analysis. Covariates were introduced into the model as either continuous or categorical functions. The influence of body weight, age, and laboratory values was treated as a continuous function, while other covariates (such as gender) were treated as categorical functions. The continuous covariates were centered on the median value of the population in the analysis. Once a full model was developed which incorporated all likely covariates, each covariate was in turn examined by removing one by one to confirm statistical significance (backward selection) using criterion of the ΔOBJ with 3.84 ($P < 0.05$). The final population pharmacokinetic model was defined by the covariates that were retained.

In order to confirm that the final model actually reflects the observed plasma concentrations, the predicted values were plotted versus the observed values and weighted residual plots for the final model.

The accuracy and robustness of the final model were assessed using a stratified non-parametric bootstrap procedure [11, 22]. Two-hundred replicate data sets were generated by random sampling with replacement and were stratified by population (healthy volunteers and patients) using the individual as the sampling unit. Population parameters for each data set were subsequently estimated using the final model. The mean parameter estimates obtained from 200 bootstrap replications were compared with those obtained from the original data set.

Model implications

The final estimated CL/F of aprepitant in typical individuals (value of η set to zero) from specific demographics was used to perform a sensitivity analysis [24] to measure the impact of important covariates on CL/F. As the first step of this evaluation, CL/F in typical patients who were not affected by any covariates was calculated. Then, CL/F in the typical population with one covariate was calculated for each covariate. On this occasion, for the continuous covariates, CL/F was calculated at the upper and lower limit of 90% confidence interval in patients. The impacts of covariates were visually shown by plotting these values on a graph.

Results

Data description

Table 3 summarizes demographic backgrounds for the population participating in aprepitant and dexamethasone

Table 3 Baseline characteristics of population pharmacokinetic analysis for aprepitant and dexamethasone

Characteristic	Aprepitant		Dexamethasone	
	Median or n	Range	Median or n	Range
Gender (male/female)	246/69		333/107	
Body weight (kg)	58.0	32.5–93.0	57.5	32.5–93.0
Age (years)	62	20–80	63	23–80
Albumin (g/dL)	3.9	1.7–5.3	3.9	1.7–5.3
AST (IU/L)	20	9–77	20	9–77
ALT (IU/L)	17	4–77	17	4–98
Total bilirubin (mg/dL)	0.50	0.20–2.20	0.50	0.20–2.20
BUN (mg/dL)	13.8	6.0–26.1	13.5	5.4–27.7
Serum creatinine (mg/dL)	0.79	0.4–1.49	0.78	0.36–1.55
Creatinine clearance (mL/min)[a]	47.8	15.3–113.4	45.3	11.7–113.4
Smoking histry (non-smoker/smoker)	232/83		310/130	

[a] Creatinine clearance was calculated on the basis of the equation of Cockcroft and Galt [6]

analysis. For aprepitant, a total of 25 healthy volunteers and 290 patients were enrolled in the analysis. The study population comprised 246 males and 69 females. The age ranged from 20 to 80 years old, with a median age of 62 years old. The background for the dexamethasone study was similar. A total of 897 and 847 drug concentration measurements were used for the population pharmacokinetic analysis for aprepitant and dexamethasone, respectively. Typical concentration time course data for aprepitant and dexamethasone are depicted in Fig. 1.

Population pharmacokinetics of aprepitant

For aprepitant, concentration time courses were best described by a one-compartment model with first-order absorption. This model used a basic structural model, and additional pharmacokinetic parameters such as t_{lag}, random variables for inter-individual variability and covariates were added stepwise to develop the population model. The t_{lag} was a necessary component to the model because its incorporation significantly improved fitting ($\Delta OBJ = 25.2$, $P < 0.001$). Inter-individual variability was needed for the parameters CL/F, V_d/F, and K_a , and was best described using a proportional error model. The covariance between CL/F and V_d/F was also needed. Intra-individual variability was also best described using a proportional error model. Next, covariates affecting the pharmacokinetics of aprepitant were explored. We found that body weight, age, ALT, BUN and aprepitant dose had significant effect on the CL/F. Body weight also had a significant effect on the V_d/F. None of the other covariates had any significant effect. Table 4 shows the parameter estimates of the final regression model. The final regression model is presented below:

$$\text{CL/F (L/h)} = \text{TVCL} \times (\text{BW}/58)^{\theta_{\text{BW1}}} (\text{AGE}/62)^{\theta_{\text{age}}} \times (\text{ALT}/17)^{\theta_{\text{ALT}}} \times (\text{BUN}/13.8)^{\theta_{\text{BUN}}} \times \text{APD}_{40}$$

$$V_d/\text{F(L)} = \text{TV}V_d \times (\text{BW}/58)^{\theta_{\text{BW2}}}$$

$$K_a(h^{-1}) = \text{TV}K_a$$

$$t_{lag}(h) = \text{TV}t_{lag}$$

where APD_{40} denotes the effects by aprepitant at the dose of 40 mg.

The inter-individual variability in the CL/F, V_d/F, and K_a were 53.9, 21.0, and 141%, respectively. The intra-individual variability was 27.7%.

Population pharmacokinetics of dexamethasone

A one-compartment model was used as a basic structural model for dexamethasone. The inter-individual variability was needed for the parameters CL and V as a proportional error model. The covariance between CL and V_d was also needed. The intra-individual variability was also best described using a proportional error model. In the investigation of covariates, we found that age, albumin, and aprepitant dose had significant effect on CL. Also, body weight had significant effect on the V_d. None of the other covariates had any significant effect. Table 5 shows the parameter estimates of the final regression model. The final regression model is presented below:

$$\text{CL (L/h)} = \text{TVCL} \times (\text{AGE}/63)^{\theta_{age}} \times (\text{ALB}/17)^{\theta_{\text{ALB}}} \times \text{APD}_{40} \times \text{APD}_{125}$$

$$V_d \text{ (L)} = \text{TV}V_d \times (\text{BW}/57.5)^{\theta_{\text{BW}}}$$

where APD_{40} and APD_{125} denotes the effects by aprepitant at the dose of 40 and 125 mg, respectively.

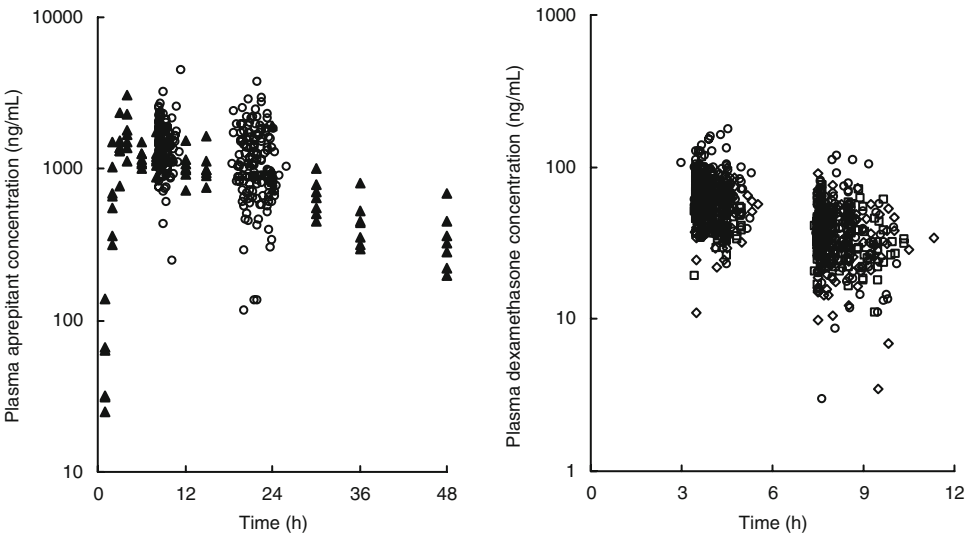

Fig. 1 Typical concentration time course data for aprepitant and dexamethasone. Individual aprepitant plasma concentrations when aprepitant 125 mg was administered to healthy volunteers (*filled triangle*) and patients (*open circle*) are shown in the *left* graph. For dexamethasone, individual plasma concentrations in the placebo group (dexamethasone 12 mg; *open circle*), 40/25-mg group (dexamethasone 8 mg; open diamond), and 125/80-mg group (dexamethasone 6 mg; *open square*) collected in a Phase II trial are shown in the *right* graph

Table 4 Parameter estimates of aprepitant from the basic model (covariate-free), final model, and results of the bootstrap analysis

Fixed effect	Basic model Mean ± SE	Final model Mean ± SE	Bootstrap Mean ± SE	Difference[a] (%)
TVCL (L/h)	2.31 ± 0.157	1.54 ± 0.118	1.56 ± 0.139	−1.2
TVV_d (L)	72.9 ± 2.37	72.1 ± 1.97	71.9 ± 2.11	0.3
TVK_a (h^{-1})	0.843 ± 0.0973	0.893 ± 0.0929	0.869 ± 0.104	2.7
TVt_{lag} (h)	0.303 ± 0.0488	0.295 ± 0.0457	0.329 ± 0.0802	−11.7
APD_{40}^{b} on CL/F	–	1.91 ± 0.161	1.92 ± 0.192	−0.8
BW on CL/F	–	0.848 ± 0.253	0.817 ± 0.350	3.7
AGE on CL/F	–	-0.361 ± 0.0784	-0.377 ± 0.103	−4.4
ALT on CL/F	–	-0.167 ± 0.0761	-0.172 ± 0.0895	−2.8
BUN on CL/F	–	0.439 ± 0.142	0.388 ± 0.190	11.9
BW on V_d/F	–	0.851 ± 0.173	0.830 ± 0.204	2.5
Inter-individual variability	Mean ± SE (CV%)	Mean ± SE (CV%)	Mean ± SE	Difference[a] (%)
$\omega^2_{CL/F}$	0.645 ± 0.177 (80.3%)	0.291 ± 0.0875 (53.9%)	0.291 ± 0.0888	0.0
$\omega^2_{V/F}$	0.0489 ± 0.0142 (22.1%)	0.0442 ± 0.0153 (21.0%)	0.0419 ± 0.0171	5.4
$\omega^2_{K_a}$	1.71 ± 0.252 (131%)	1.99 ± 0.339 (141%)	1.84 ± 0.438	7.3
$\omega_{CL/F\ V/F}$	0.0679 ± 0.0364	0.0607 ± 0.0136	0.0553 ± 0.0137	9.1
σ^2	0.0713 ± 0.00996 (26.7%)	0.0770 ± 0.00975 (27.7%)	0.0779 ± 0.0116	−1.3

TVCL typical value of oral clearance, TVV_d typical value of apparent distribution volume, TVK_a typical value of absorption rate, TVt_{lag} typical value of absorption lag time, *BW* body weight

[a] (Bootstrap value–final model value)/final model value × 100%

[b] APD_{40} is multiplied to the TVCL when aprepitant dose is 40 mg (The CL/F of aprepitant at the doses of 80 and 125 mg is 47.6% lower than the 40 mg aprepitant.)

The inter-individual variability in the CL and V_d were 40.2 and 22.6%, respectively. The intra-individual variability was 7.5%.

Final model evaluation

In order to confirm that the final model of aprepitant and dexamethasone actually reflects the observed plasma concentrations, the predicted values are plotted versus the observed values and weighted residual plots for the final models (Fig. 2). For aprepitant and dexamethasone, the residuals were generally distributed around zero and were relatively symmetric. No obvious bias pattern was apparent in the plot of the predicted concentration versus the weighted residual.

Tables 4 and 5 list the parameter estimates of the basic models, final models and the results of the bootstrap validation step. Successful convergence of the 200 bootstrap samples was achieved in 196 cases for aprepitant, and 168 samplings for dexamethasone. It was defined to be successfully converged when a successful covariance step was obtained in a NONMEM analysis. All structural parameters, as well as the variance parameters for aprepitant and dexamethasone, were within 15% of the bootstrapped mean.

Model implications

The sensitivity analysis results of aprepitant at the dose of 125 mg are shown in Fig. 3, which depict the effects of body weight, age, BUN, and ALT on the CL/F. Each bar represents the influence of a single covariate on typical CL/F (value of η set to zero). The most influential covariate is shown at the top of the plot. The solid line represents the CL/F in a typical 57.9 kg, 63-year-old, Japanese patients with a BUN of 14.0 and an ALT of 1.54.

Discussion

There was no significant difference in CL/F between 80 and 125 mg dose of aprepitant, but CL/F at the dose of 40 mg was 1.9 times higher than those at the other two dose, which may be because aprepitant is eliminated from the body mainly via CYP3A4-mediated metabolism [10] and the enzyme becomes partially saturated as the dose increases. Among intrinsic factors, the covariate that affected CL/F most was body weight; specifically, CL/F was elevated as body weight increased. However, based on the result of a Phase II study in which body weight was not shown to affect the safety and efficacy of aprepitant (in-

Table 5 Parameter estimates of dexamethasone from the basic model (covariate-free), final model, and results of the bootstrap analysis

Fixed effect	Basic model Mean ± SE	Final model Mean ± SE	Bootstrap Mean ± SE	Difference[a] (%)
TVCL (L/h)	9.85 ± 0.247	13.3 ± 0.448	13.3 ± 0.490	0.1
TVV_d (L)	86.8 ± 1.26	86.1 ± 1.14	86.0 ± 1.23	0.1
APD^b_{40} on CL	–	0.753 ± 0.0385	0.754 ± 0.0362	−0.1
APD^c_{125} on CL	–	0.525 ± 0.0293	0.528 ± 0.0313	−0.5
AGE on CL	–	−0.325 ± 0.119	−0.336 ± 0.135	−3.4
ALB on CL	–	−0.497 ± 0.144	0.468 ± 0.176	5.9
BW on V_d	–	0.626 ± 0.0732	0.622 ± 0.0724	0.7
Inter-individual variability	Mean ± SE (CV%)	Mean ± SE (CV%)	Mean ± SE	Difference[a] (%)
ω^2_{CL}	0.265 ± 0.0222 (80.3%)	0.162 ± 0.0154 (40.2%)	0.162 ± 0.0138	−0.2
$\omega^2_{V_d}$	0.0888 ± 0.0299 (22.1%)	0.0509 ± 0.0162 (22.6%)	0.0535 ± 0.0116	−5.1
$\omega_{CL}V_d$	0.0737 ± 0.0152	0.0626 ± 0.00960	0.0629 ± 0.00821	−0.5
σ^2	0.00819 ± 0.00482 (9.0%)	0.00561 ± 0.00429 (7.5%)	0.00429 ± 0.00291	11.1

TVCL typical value of clearance, *TVV_d* typical value of distribution volume, *TVK_a* typical value of absorption rate, *ALB* albumin, *BW* body weight

[a] (Bootstrap value–final model value)/final model value × 100%

[b] APD_{40} is multiplied to the TVCL of dexamethasone when 40 mg aprepitant is co-administered. (The CL of dexamethasone co-administered with 40 mg aprepitant is 24.7% lower than dexamethasone alone.)

[c] APD_{125} is multiplied to the TVCL of dexamethasone when 125 mg aprepitant is co-administered. (The CL of dexamethasone co-administered with 125 mg aprepitant is 47.5% lower than dexamethasone alone.)

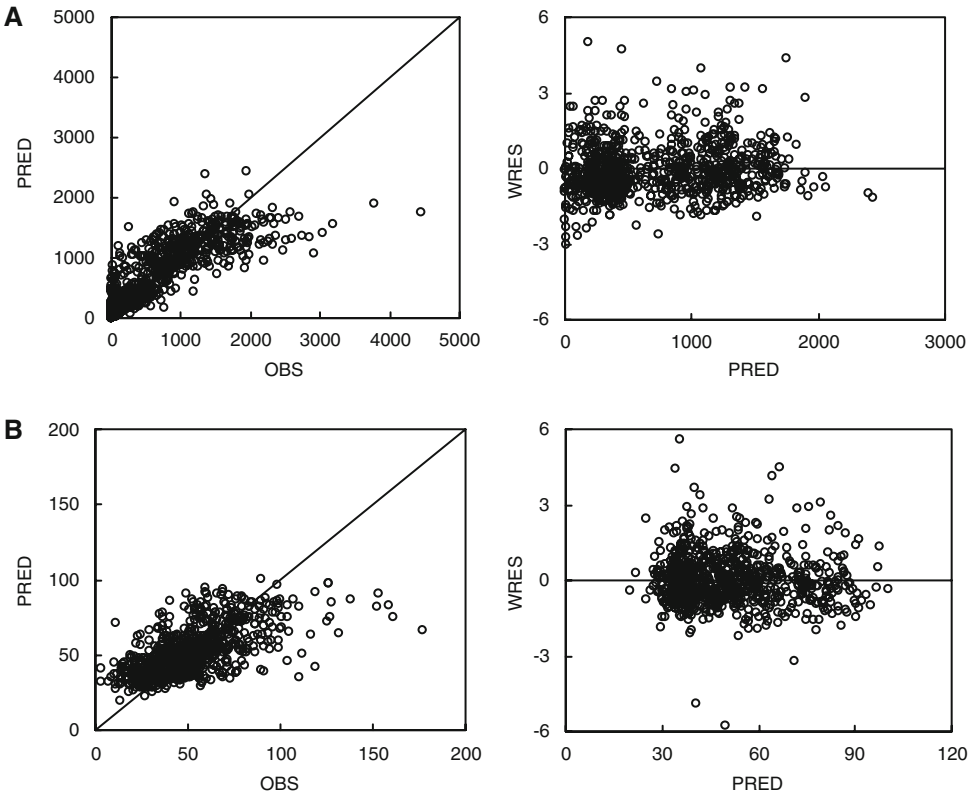

Fig. 2 Predicted (PRED) versus observed (OBS) plasma concentrations and weighted residuals (WRES) versus predicted plasma concentrations from the final model. **a** and **b** show the results of aprepitant and dexamethasone, respectively

house data), the changes in pharmacokinetics caused by body weight may not be clinically significant. Other factors that affected CL/*F* of aprepitant included age, a parameter of hepatic function (ALT) and a parameter of renal function (BUN). CL/*F* decreased as ALT level increased, probably because the metabolic capacity of the liver to

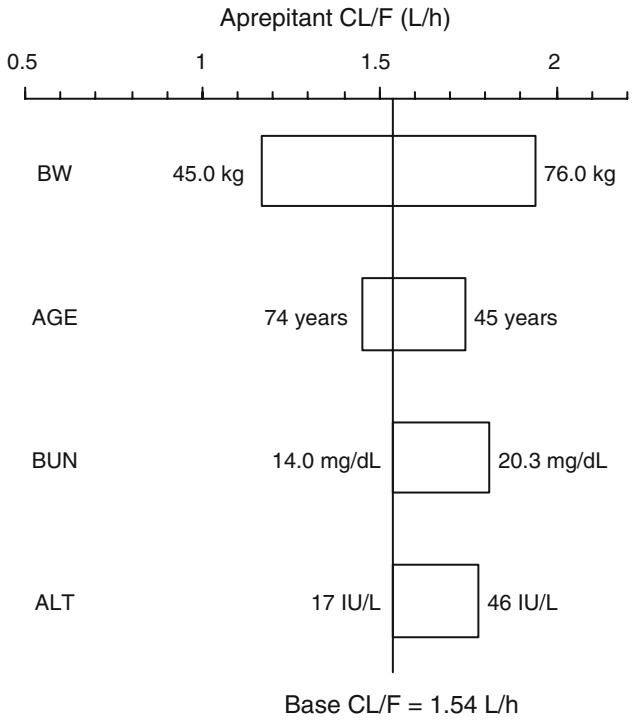

Fig. 3 Sensitivity plot comparing the effect of covariates on apparent clearance (CL/*F*) of aprepitant. The *solid vertical line* is the CL/*F* in a typical Japanese cancer patient. The *label* at each end of the *bar* represents the participant characteristic. The length of each bar describes the CL/F changes for typical individuals with specified demographics

break down aprepitant is decreased due to hepatic dysfunction. The increase in CL/*F* accompanying the increase in BUN could be attributed to the low plasma albumin concentration (due to nephropathy) and the competitive inhibition of plasma protein binding by endogenous substances. The effect of ALT and BUN increase on CL/*F* was negligible in the population of this study, considering that CL/*F* change was within 20%. It has been described in the package insert of aprepitant that the AUC of aprepitant on patients with moderate hepatic insufficiency was 10% higher than healthy subjects, and the difference is not considered clinically meaningful [10]. Our results were considered to be consistent with that description. However, caution should be exercised when aprepitant is administrated in patients with severe hepatic dysfunction as described in the package insert, while it has been reported that severe renal insufficiency and haemodialysis did not alter the aprepitant pharmacokinetics in a clinically meaningful manner [3]. These reports are as expected, given that aprepitant is cleared by hepatic metabolism rather than renally excreted.

In the Phase II study, aprepitant was administered (to prevent CINV) along with the standard therapeutic agents, steroid (intravenous dexamethasone) and 5HT3 antagonist (intravenous granisetron). Aprepitant has been reported not to affect the pharmacokinetics of 5HT3 antagonists [4, 15, 23]. In contrast, aprepitant moderately inhibits CYP3A4, which is involved in the metabolism of dexamethasone. McCrea et al. [19] reported that the CL of dexamethasone was decreased approximately 54% by co-administrating 125 mg aprepitant with its oral dexamethasone. Therefore, in this study we evaluated how aprepitant affects the pharmacokinetics of intravenous dexamethasone. When aprepitant was administered at daily doses of 40 and 125 mg, CL of intravenous dexamethasone decreased 24.7 and 47.5%, respectively, which was consistent with the previous report [19]. However, the result of the present study, which demonstrated the comparable effects of aprepitant on CL of intravenous and oral dexamethasone, disaccords with that of the study conducted for midazolam, which suggested greater influence of aprepitant on oral midazolam than on intravenous midazolam. Co-administration of aprepitant 125 mg increased AUC of intravenous and oral midazolam by 1.47- and 2.27-fold, respectively [18]. The difference observed in these substrates, dexamethasone and midazolam, could be explained by the difference in the extent of their first pass effects. Bioavailability of dexamethasone and midazolam are approximately 75 and 30%, respectively [18, 19, 25]. Consequently, the effects of aprepitant on CL of intravenous and oral dexamethasone were found to be similar in our analysis likely because the aprepitant did not significantly affect the first pass effect of oral dexamethasone. The results of our study in Japanese subjects suggest that, for aprepitant therapy at dose-regimen of 125/80 mg, it may be appropriate to reduce the dose of intravenous dexamethasone by up to half, as in the case of oral dexamethasone [10]. This conclusion is limited by the fact that only two time points were utilized in the present population pharmacokinetic model. Full pharmacokinetic evaluations with other CYP3A4 substrates, methylprednisolone and midazolam (discussed above), have indicated that the magnitude of CYP3A4 inhibition by aprepitant is greater for oral versus intravenous dosing of these drugs [18, 19].

Because the dose-concentration relationship of aprepitant was non-linear between the doses of 40 and 125 mg, data from the Phase I study were necessary to evaluate the covariates appropriately. When the data from the Phase I study were excluded from this analysis, despite the obvious effect of aprepitant dose on CL/F, such an effect was not detected. Therefore, the data on aprepitant from the Phase I study were included in this analysis. The results of diagnostic plot and bootstrap validation of our final model suggest that the population pharmacokinetic model we constructed in this study is reliable and robust.

The full pharmacokinetic profile of intravenous dexamethasone has been reported by Varis et al. [25]. According to this report, CL and V_d of dexamethasone

determined by moment analysis were approximately 14.6 L/h and 84 L (as calculated for the body weight of 60 kg), respectively. The typical CL and V_d estimated by using our final model were 13.3 L/h and 86.1 L, respectively, quite consistent with those reported by Varis.

In summary, we developed a pharmacokinetic model for aprepitant that incorporates body weight, age, ALT, BUN and aprepitant dose to predict CL/*F*. The results of population pharmacokinetic analysis of dexamethasone supported the dose reduction of dexamethasone in the case of its co-administration with aprepitant.

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