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ARTICLE

Pharmacokinetics of Oxycodone After Intravenous and Subcutaneous Administration in Japanese Patients with Cancer Pain

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ABSTRACT

In Japan, Oxycodone hydrochloride injection formulation has been approved in 2012. However, its pharmacokinetics has been poorly studied. The aim of this study is to evaluate the pharmacokinetics of oxycodone after intravenous and subcutaneous administration of oxycodone hydrochloride injection in Japanese patients with cancer pain. Noncompartmental analysis and population pharmacokinetic analysis were performed. We conducted a multicenter open-label study of oxycodone hydrochloride administered as constant infusion with the dose titrated individually according to the pain intensity in patients with cancer pain. Pharmacokinetic parameters for plasma oxycodone and its metabolites were estimated using pharmacokinetics of oxycodone was evaluated using a total of 344 plasma concentrations obtained from 89 patients. The estimated geometric mean clearance (CL) of oxycodone was 24.3 L per hour after constant intravenous infusion and 29.5 L per hour after constant subcutaneous infusion, respectively. Population pharmacokinetic analysis indicated that body surface area was the influencing factor on CL and there were no pharmacokinetic differences for CL between intravenous and subcutaneous infusion. These results provide important information for the clinical use of oxycodone injection.

KEYWORDS Oxycodone, drug concentration, NONMEM, cancer pain, population pharmacokinetics

INTRODUCTION

Oxycodone is a semi-synthetic μ-opioid receptor agonist which is derived from the opium alkaloid, thebaine, and has been in clinical use as analgesic drug which is effective for the relief of moderate to severe pain since 1917. Parenteral oxycodone formulations are used mainly for the treatment of acute postoperative pain and controlled-release tablet is used to manage cancer-related pain and chronic noncancer-related pain.[1] Following oral administration, the absolute bioavailability of oxycodone is over 60%.[2,3] The metabolism of oxycodone in human is still poorly characterized. The main known metabolic pathways of oxycodone are via N-demethylation to noroxycodone and by way of O-demethylation to oxymorphone.[1]

In Japan, oxycodone hydrochloride controlled-release tablets and immediately-release powder were approved in 2003 and 2007, respectively, and have been used for patients with cancer pain.[4,5] For patients with chronic cancer pain, treatment with oral analgesics is considered most convenient and feasible. The oral route, however, is difficult to be used for the patients with hard swallowing, nausea, vomiting, and gastrointestinal obstruction. Oxycodone hydrochloride injection formulation as alternative route has developed for these patients with cancer pain and was approved in 2012. Pharmacokinetic information of oxycodone after bolus injection or constant

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TABLE 1. Summary of clinical study design

Summary of study	Intravenous administration study		Subcutaneous administration study
Study design	Multiple-center, open-label, dose ascending		Multiple-center, open-label, dose ascending
Population	Japanese patients with cancer pain		Japanese patients with cancer pain
Dosing regimen	Bolus intravenous administration	Constant intravenous infusion	Constant subcutaneous infusion
Sampling times	0, 5, and 10 minutes, 1, 2, 4, and 6 hours	0, 2, 4, 6, 8, and 12 hours, and one point at steady state	0, 2, 4, 6, 8, and 12 hours, and one point at steady state
Number of subject [at the start of infusion, at steady state]	11 [11, –]	69 [10, 69]	20 [20, 18]
Number of conc. data [at the start of infusion, at steady state]	77 [77, –]	129 [60, 69]	138 [120, 18]
Number of subject (Number of conc. data) for Population PK	–	69 (119 points) 10 subjects: 6 points 59 subjects: 1 point	20 (115 points) 16 subjects: 6 points 3 subjects: 5 points 1 subjects: 4 points

infusion is limited for not only Japanese patients with cancer pain but also patients other than Japanese.[2,3,6–10]

METHODS

Data of Clinical Studies for Pharmacokinetic Analysis

Oxycodone hydrochloride injection formulation is an aqueous solution for injection containing 10 mg/mL of oxycodone hydrochloride. The injection contains sodium citrate hydrate, citric acid hydrate, sodium chloride, hydrochloric acid, sodium hydroxide, and water for injection as excipients.

Oxycodone hydrochloride was intravenously or subcutaneously administered to Japanese patients with cancer pain in two multi-center open-label clinical studies. Cancer pain was controlled by constant infusion of oxycodone hydrochloride with dose titrated and adjusted individually based on the pain intensity and adverse event. Concomitant medications that were part of the regular therapy of the patients were permitted. Blood samples (3 mL) were collected into heparinized tubes for pharmacokinetic evaluation at predose, 5 and 10 minutes, 1, 2, 4, and 6 hours after the bolus intravenous administration, or predose, 2, 4, 6, 8, and 12 hours after the start of the constant intravenous or subcutaneous infusion, and at steady state after the constant intravenous or subcutaneous infusion. Blood samples were centrifuged, and the plasma was separated and stored frozen at −20°C until analysis

Supplemental rescue dose of morphine were allowed at the start of administration and supplemental rescue dose of oxycodone were allowed to treat the cancer breakthrough pain after the pharmacokinetic sampling period (i.e., 6 hours after bolus administration, 12 hours after the start of infusion). The rescue doses of 1-hour infusion volume (1/24 of daily dose) were administrated at one time via the same intravenous or subcutaneous route.

Table 1 summarizes the study designs, dosing regimens, number of subject, and number of plasma oxycodone concentration data of those clinical studies. The 69 and 20 patients were involved in the intravenous administration study and subcutaneous administration study, respectively. The 11 of 69 patients in the intravenous study were involved in the pharmacokinetic evaluation after bolus intravenous administration before constant intravenous infusion. One plasma sample was excluded from summarized data and the pharmacokinetic analysis because of outlier decided in visual inspection. This sample was described and discussed in detail in discussion section. After exclusion of one plasma sample, numbers of observed plasma concentration data were 77, 129, and 138 after intravenous bolus administration, constant intravenous infusion, and constant subcutaneous infusion, respectively.

Patients' demographics (age, BWT and BSA etc.) were summarized in (Table 2). Demographic data were similar between the intravenous administration study and subcutaneous administration study. Of 69 patients in the intravenous administration study, 17 kinds of solid cancer patients such as lung cancer ($n = 19$), colon cancer ($n = 11$), pancreatic cancer ($n = 5$), gastric cancer ($n = 5$), and multiple cancer of which primary cancer was unknown ($n = 7$) were included. The score of performance status (PS) were 1 to 3 and 4 in 88.4% ($n = 61$) and 8.7%

TABLE 2. Summary of demographic data

Number of subjects		Age (years old)	BWT (kg)	Height (cm)	BSA (m^2)	Scr (mg/dL)	CLcr (mL/min)	AST (IU/L)	ALT (IU/L)
Intravenous	Mean	65	52.5	160	1.53	0.84	67.7	34	29
administration study	SD	10	11.7	10	0.19	0.29	25.8	34	36
Total 69	Minimum	35	28.2	141	1.10	0.39	23.7	10	5
Male 44	Median	66	51.3	160	1.51	0.80	63.5	21	17
Female 25	Maximum	84	81.5	186	2.06	2.11	131.5	171	175
Subcutaneous	Mean	67	54.0	161	1.55	0.72	78.6	28	33
administration study	SD	12	12.4	8	0.19	0.15	32.3	21	25
Total 20	Minimum	44	32.5	144	1.18	0.42	31.4	11	9
Male 15	Median	68	54.0	164	1.59	0.71	80.5	24	32
Female 5	Maximum	87	76.1	173	1.85	1.08	157.4	112	111
All subjects	Mean	66	52.8	160	1.53	0.81	70.2	33	29.9
	SD	10	11.8	9	0.19	0.27	27.6	32	33.4
Total 89	Median	67	51.7	161	1.53	0.77	65.5	22	19

BWT: Body weight, BSA: Body surface area, Scr: serum creatinine, CLcr: creatinine clearance
AST: aspartate aminotransferase, ALT: alanine aminotransferase

($n = 6$) of these patients, respectively. Of 20 patients in subcutaneous administration study, eight kinds of solid cancer patients such as lung cancer ($n = 9$), colon cancer ($n = 4$), and gastric cancer ($n = 2$) were included. The score of PS were 1 to 3 and 4 in 95% ($n = 19$) and 5% ($n = 1$) of these patients, respectively.

All clinical studies were approved by the ethics committees for each site and conducted in compliance with the Declaration of Helsinki and all participants gave written informed consent before screening.

Determination of Oxycodone, Noroxycodone, and Oxymorphone in Plasma

Oxycodone and its metabolites, noroxycodone, and oxymorphone in plasma were determined by the liquid chromatography-tandem mass spectrometric (LC/MS/MS) method. The LC/MS/MS system used consisted of a HPLC pump LC-20ADXR and LC-20AD (Shimadzu corporation, Japan), an autosampler SIL-20ACXR (Shimadzu corporation, Japan), a column oven CTO-20AC (Shimadzu corporation, Japan), and a mass spectrometer API5000™ (Applied Biosystems™, CA, USA). The data were analyzed by Analyst® (ver.1.5, Applied Biosystems™, CA, USA).

The analytical column was XBridge™ C18 (Waters Corporation, MA, USA) column (2.1 mm I.D. × 100 mm, 3.5 μm particles). A linear gradient system was applied. Mobile phase A was 5 mmol/L ammonium formate (pH 9.4) and mobile phase B was acetonitrile. The 70% A and 30% B was maintained for 2 minutes and linear gradient was applied from 70% A and 30% B to 30% A and 70% B over 3 minutes and then returned immediately to 70% A and 30% B and maintained for 6 minutes. The flow rate was 0.2 mL/min and total run time was 11 minutes. Mass spectrometer API5000™ was equipped with an electrospray interface and used in positive mode for quantitative multiple reaction monitoring. The voltage over the capillary was kept at 4000 V. The temperature of the nitrogen drying gas was set to 700°C

After addition of the internal standard, oxycodone-d_6, noroxycodone-$^{13}Cd_3$, and oxymorphone-$^{13}Cd_3$ synthesized by Shionogi & Co., Ltd., samples were applied onto a solid phase extraction column OASIS HLB, 60 mg/3 cc (Waters corporation, MA, US). The final elute was evaporated to dryness under a stream of nitrogen gas at 40°C and the residue was dissolved with 60 μL of 20% acetonitrile. A 4 μL aliquot of reconstituted solution was injected into the LC/MS/MS system. The monitoring ions set for each compounds are as follows: m/z 316.3 to 241.2 for oxycodone, m/z 322.1 to 247.1 for oxycodone-d_6, m/z 302.3 to 227.1 for noroxycodone, m/z 306.3 to 231.1 for noroxycodone-$^{13}Cd_3$, m/z 302.2 to 227.1 for oxymorphone and m/z 306.2 to 231.1 for oxymorphone-$^{13}Cd_3$. They were resolved at around 5.8 minutes for oxycodone, 2.1 minutes for noroxycodone, and 3.1 minutes for oxymorphone.

The lower limits of quantification were 0.100 ng/mL for oxycodone, noroxycodone, and oxymorphone. The intra-day coefficient of variations were less than 12.9%, 11.7%, and 4.9%, and inter-day coefficient of variations were 13.2%, 9.6%, and 7.2% for oxycodone, noroxycodone, and oxymorphone, respectively.

TABLE 3. Summary of pharmacokinetic parameters of oxycodone by noncompartmental analysis

Number of subjects (Samples)			$AUC_{0\text{-}6hr}$ (ng.hr/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	$t_{1/2,z}$ (hr)	CL (L/hr)
Bolus intravenous administration		Geometric Mean	95.62	131.1	3.22	34.2
		Geometric CV (%)	25.6	36.4	20.4	36.3
Total	11 (77)	Minimum	59.65	71.33	2.49	17.8
Male	6 (42)	Median	103.1	142.2	3.20	31.5
Female	5 (35)	Maximum	122.8	252.3	4.41	62.8

AUC were adjusted to 5 mg administration of oxycodone hydrochloride, respectively.

Pharmacokinetic Analysis

Pharmacokinetic parameters for plasma oxycodone and its metabolites, noroxycodone and oxymorphone, were estimated using noncompartmental analysis. In addition, population pharmacokinetic analysis of oxycodone was performed using observed plasma oxycodone concentration data. Noncompartmental analysis and population pharmacokinetics were performed using the actual titrated dose. In summary statistics and figures (Tables 3 and 4, and Figures 1 and 4), plasma concentrations and AUC were adjusted to 5 mg oxycodone hydrochloride dose (actual dose in the study: 2–10 mg) in bolus intravenous administration, and were adjusted to 1 mg/hour oxycodone hydrochloride infusion rate (actual infusion rate in the study: 0.312–6 mg/hour at the start of intravenous infusion, 0.416–12 mg/hour at the start of subcutaneous infusion, 0.209–40 mg/hour at steady state after intravenous infusion, and 0.25–19 mg/hour at steady state after subcutaneous infusion) in constant intravenous and subcutaneous infusion.

Noncompartmental Analysis

Noncompartmental analysis was performed using pharmacokinetic analysis software, WinNonlin® (Ver 5.2.1, Pharsight Corporation, CA, USA). The following pharmacokinetic parameters were estimated; clearance (CL), area under the plasma concentration-time curve (AUC), and half life in the elimination phase ($t_{1/2,z}$) after bolus intravenous administration, AUC in 12 hours after the start of constant infusion, CL at steady state after constant infusion.

Population Pharmacokinetic Analysis

The population pharmacokinetic analysis was performed using a nonlinear mixed effect modeling software, NONMEM® (Version VII, ICON

TABLE 4. Summary of clearance of oxycodone and plasma concentrations of oxycodone and metabolites at steady state after constant infusion

Number of subjects (Samples)			Oxycodone CL (L/hr)	Oxycodone concentration (ng/mL)	Noroxycodone concentration (ng/mL)	Oxymorphone concentration (ng/mL)
Constant intravenous infusion		Geometric Mean	24.3	36.9	19.2	0.373
		Geomtric CV (%)	39.9	39.9	70.6	85.4
Total	69 (69)	Minimum	10.1	12.4	4.47	< 0.100
Male	44 (44)	Median	24.6	36.5	19.4	0.272
Female	25 (25)	Maximum	72.5	88.7	91.2	1.67
Constant subcutaneous infusion		Geometric Mean	29.5	30.4	14.4	0.386
		Geomtric CV (%)	31.6	31.6	67.8	81.0
Total	18 (18)	Minimum	17.3	17.9	6.38	< 0.100
Male	13 (13)	Median	28.3	31.7	12.2	0.310
Female	5 (5)	Maximum	50.2	51.7	77.8	1.63

Plasma concentrations were adjusted to 1 mg/hr oxycodone hydrochloride administration.

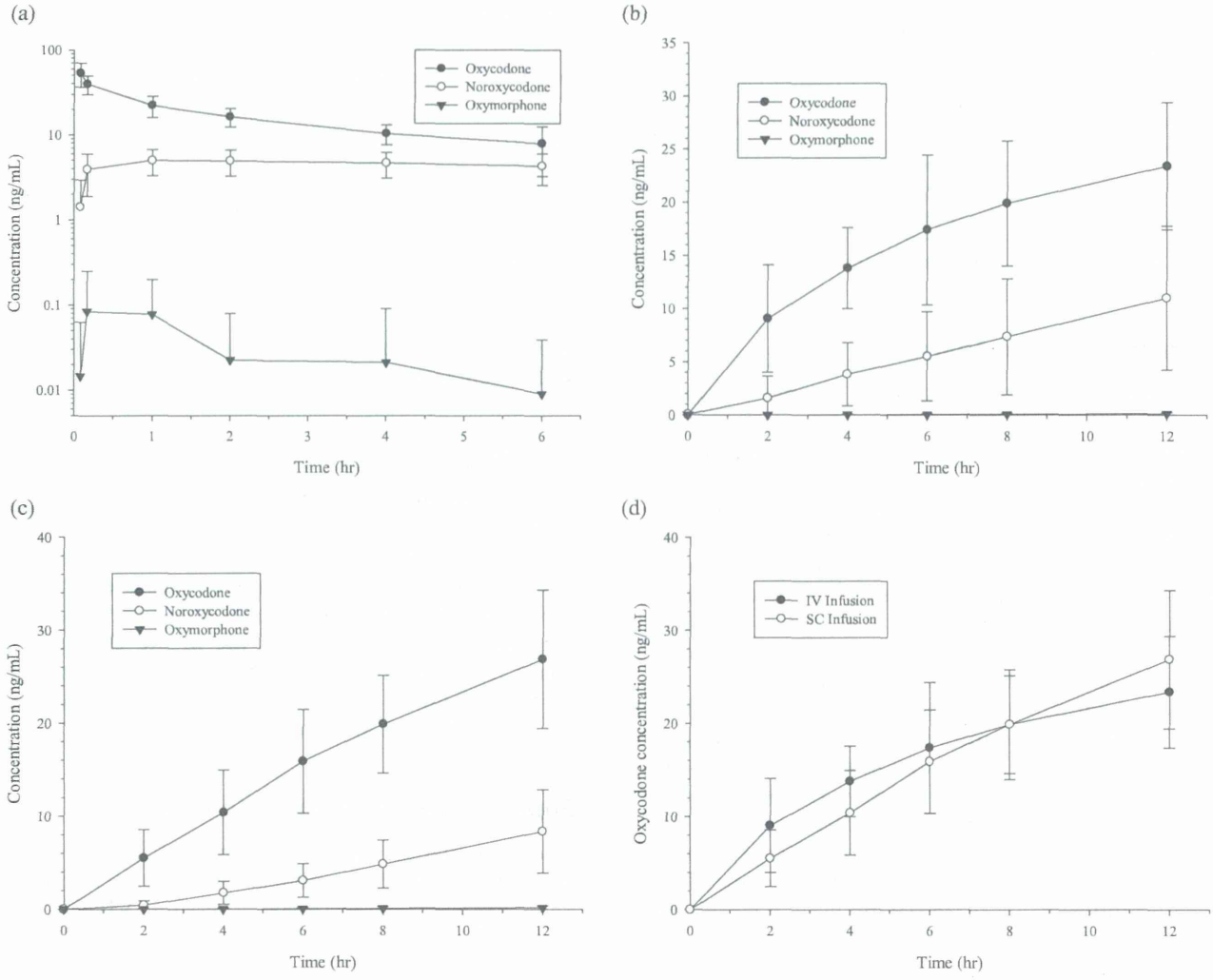

FIGURE 1. The mean with standard deviation plasma concentration profiles of oxycodone, noroxycodone, and oxymorphone after oxycodone hydrochloride (a) bolus intravenous administration, (b) constant intravenous infusion, and (c) constant subcutaneous infusion. (d) The plasma concentration profiles of oxycone after oxycodone hydrochloride constant infusion. The concentration adjusted to 5 mg of oxycodone hydrochloride dose in bolus intravenous administration and adjusted to 1 mg/hour of oxycodone hydrochloride infusion rate in constant infusion.

Development Solutions, MD, USA).[11] The first-order conditional estimation with interaction (FOCE-I) method was used for the analysis.

First, a basic population pharmacokinetic model without any covariate (base model) was evaluated. The pharmacokinetics of oxycodone was assumed to follow a one-compartment model. The subroutine ADVAN 1 was used and the basic pharmacokinetic parameters were CL and distribution volume (V). The inter-individual variability was assumed to follow a log-normal distribution for CL and V, and an exponential error model was used for the inter-individual variability. A model for an intra-individual variability was selected from an exponential error model, an additive error model and combination error model (the additive error + the exponential error model).

Next, a covariate model was constructed by forward selection procedure. The age, body weight (BWT), body surface area (BSA), sex, serum creatinine (Scr), and creatinine clearance (CLcr), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were tested as a covariate on CL, where BSA was calculated by Du Bois formula[12] and CLcr was calculated by Cockcroft & Gault formula.[13] The age, sex, and BWT were tested as a covariate on V. A power model for a continuous variable (age, BWT, BSA, Scr, CLcr, AST, and ALT) and an additive model for a categorical variable (sex)

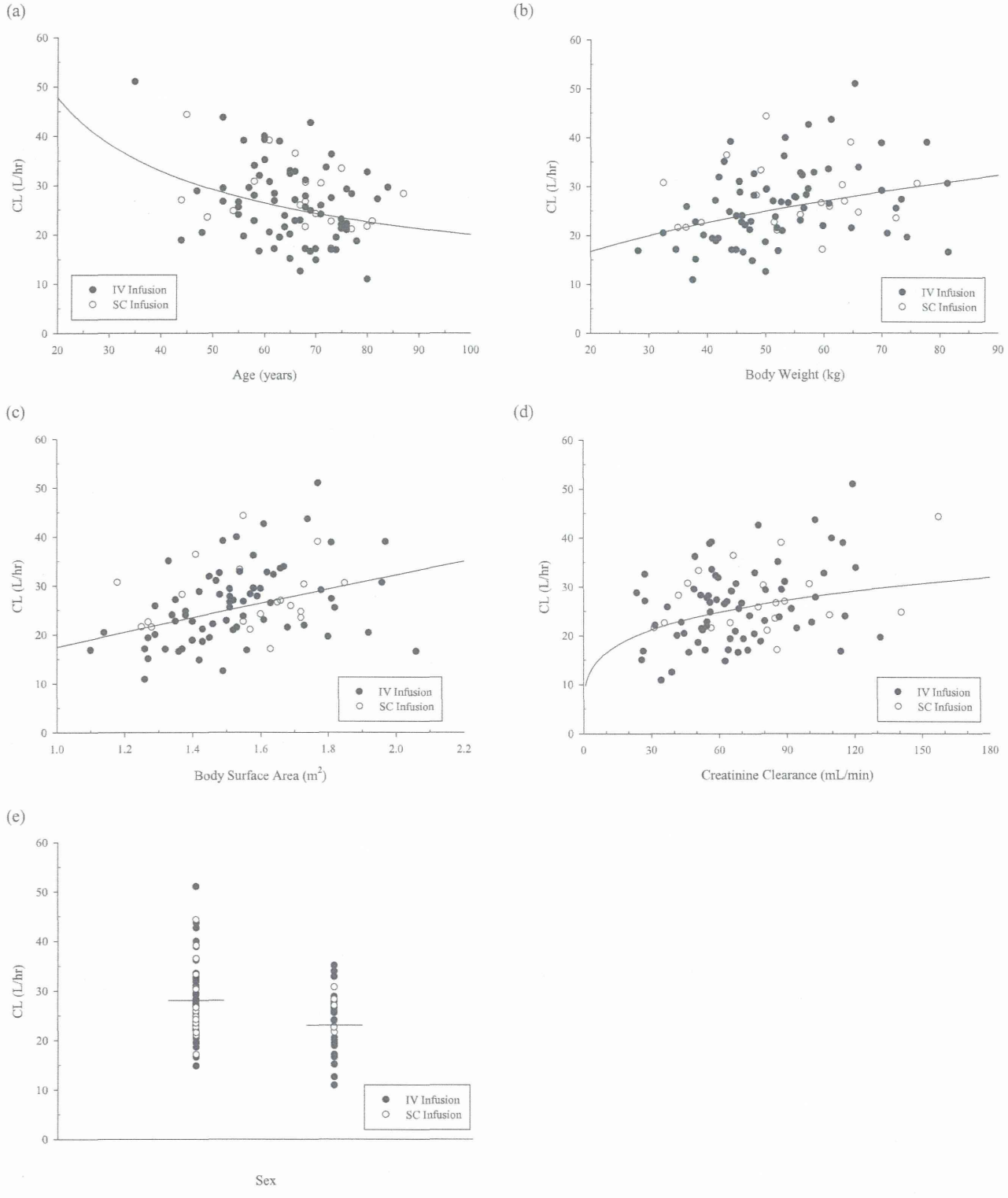

FIGURE 2. The relationships between demographics of patients and individual Bayesian-estimated clearance (CL) based on the base model, (a) age, (b) body weight, (c) body surface area, (d) creatinine clearance, and (e) sex. The plots were marked by intravenous (IV) infusion and subcutaneous (SC) infusion, separately. Least squares regressions were performed by ln(CL) versus ln(X parameter) and regression curve was indicated by exp(intercept) $\times$ (X parameter) $^{\text{slope}}$ for (a)–(d). Slope values were (a) −0.542, (b) 0.437, (c) 0.882, and (d) 0.228 and its p-values were (a) 0.004, (b) 0.001, (c) <0.001, and (d) 0.002. Mean CL were 28.1 (male) and 23.1 (female) and mean lines were indicated in (e).

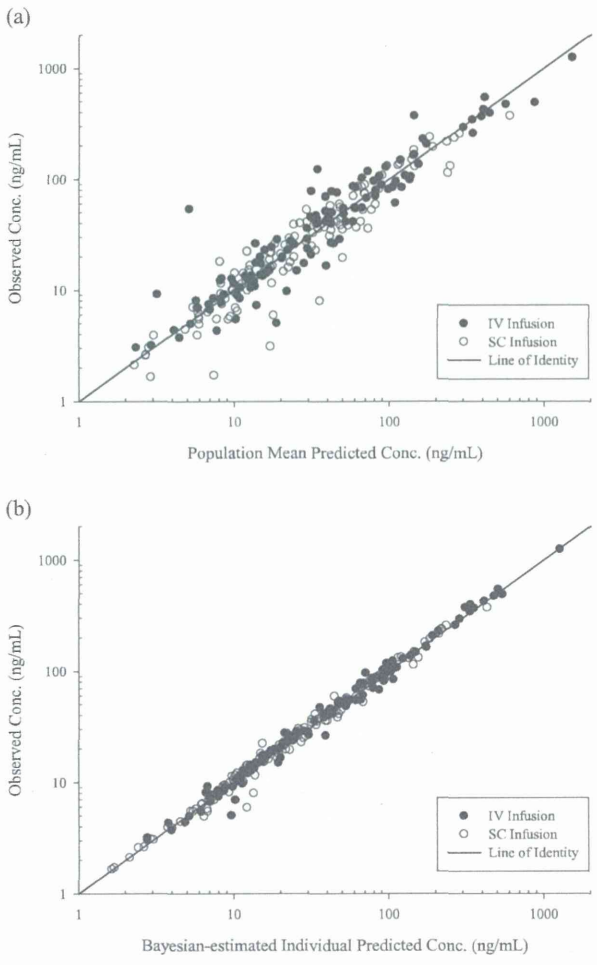

FIGURE 3. Diagnosis plots. The scatter plots for (a) the observed (DV) versus population mean predicted plasma concentrations (PRED) and (b) the observed (DV) versus Bayesian-estimated individual predicted plasma concentrations (IPRED) with a line of identity. The plots were marked by intravenous (IV) infusion and subcutaneous (SC) infusion, separately.

were used for the analysis given by the following equations.

$$\text{PKP} = \theta_1 \times (\text{COV}/\text{Median of COV})^{\theta 2} : \text{power model} \quad [1]$$

$$\text{PKP} = \theta_1 + \theta_2 \times \text{COV} : \text{additive model (COV : 0 or 1)} \quad [2]$$

where PKP is the typical PK parameter, COV is a covariate, and θ_1 and θ_2 are the parameters to be estimated. A categorical variable (sex) was treated as a binary variable (0 for male; 1 for female). The model was selected by the objective function (OBJ) obtained from NONMEM at the significance level of 5% based on χ^2 test, that is, a change in OBJ (−2 log likelihood difference, −2l.l.d.) of 3.84 with a difference in freedom of unity represents a statistically significant model improvement. After selection of covariates, the model was refined by backward elimination procedure with the significance level of 1% (ΔOBJ > 6.63) based on χ^2 test (final model).

In addition, because plasma concentration profiles after constant subcutaneous infusion seem to have the lag time from visual inspection, one-compartment model with or without a lag time for constant subcutaneous infusion were also examined on the basis of the covariate model.

Finally, the pharmacokinetic differences between constant intravenous infusion and constant subcutaneous infusion were examined by adding administration route factor to CL and V in the model as a binary variable. A proportional model was used for the evaluation of this difference,

$$\text{PKP} = \theta_1 \times (1 + \theta_2 \times \text{COV}) : \text{proportional model} \quad [3]$$

where COV is a binary variable of administration route (i.e. 0 for constant intravenous infusion and 1 for constant subcutaneous infusion). The model was also selected by the OBJ obtained from NONMEM at the significance level of 1% based on χ^2 test.

Steady-state plasma concentrations were treated to be sampled at 96 hours after constant infusion. Rescue doses within 24 hours before the blood sampling time at steady state were also considered for population pharmacokinetic analysis.

Model Evaluation

Population pharmacokinetic model was evaluated by diagnostic plots of the observed plasma concentrations versus population mean predicted plasma concentrations and the observed plasma concentrations versus Bayesian-estimated individual predicted plasma concentrations. In addition, the nonparametric bootstrap re-sampling procedure was applied to assess the stability of the final parameter estimates and to confirm the robustness of the final model[14] using Wings for NONMEM.[15] One thousand bootstrap sample sets were re-sampled from the original data set. Then, parameters for each of the 1000 sample sets were estimated using the final model. The median and 95% confidence intervals (CI), obtained as the 25th and 975th smallest values out of 1000 parameters estimated from bootstrap sample sets, were compared with the mean and 95% CI, derived from

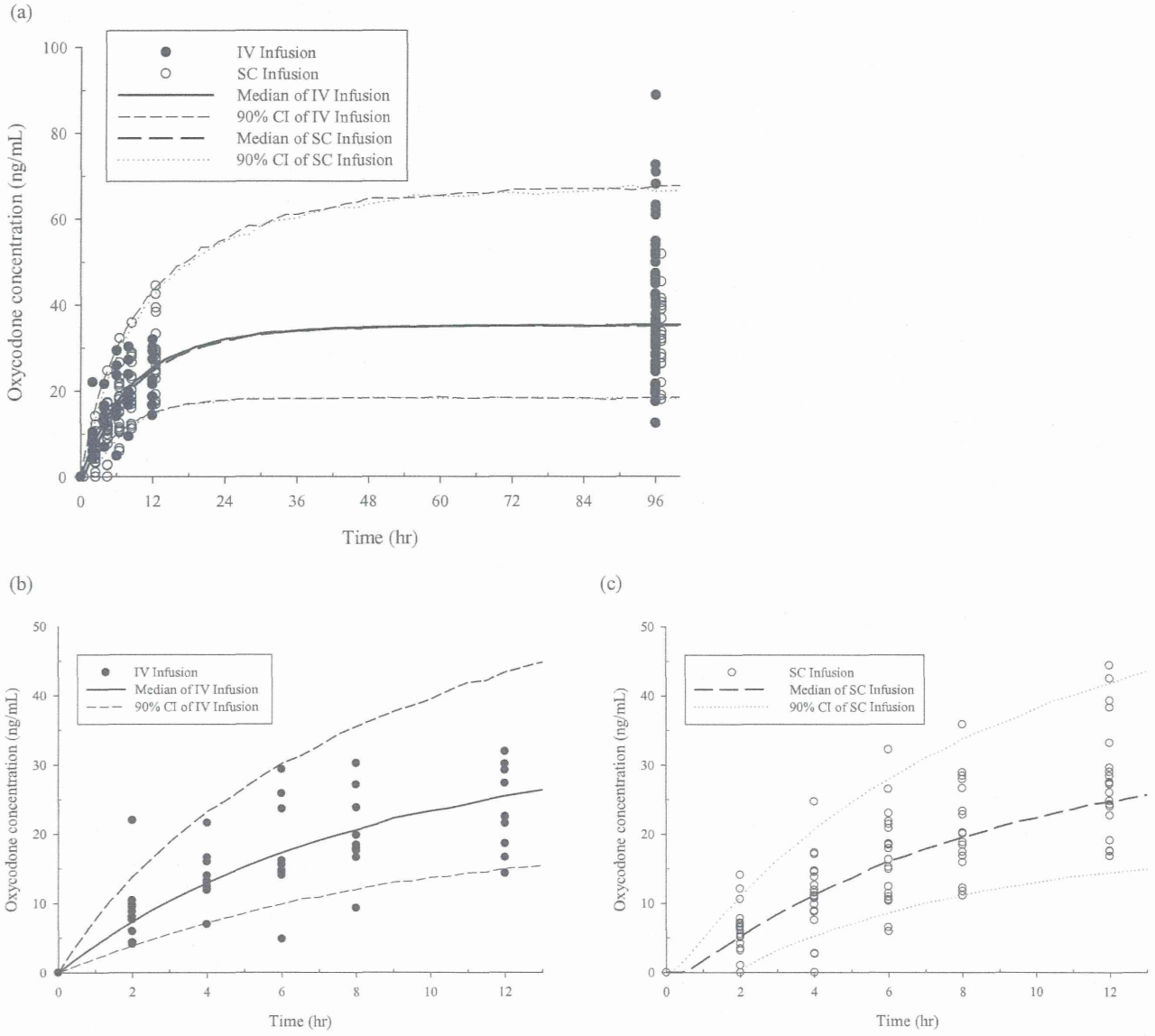

FIGURE 4. Observed plasma oxycodone concentration with median and 90% CI profiles. The observed plasma oxycodone concentrations were compared with median and 90% CI simulated on the basis of the final model by Monte-Carlo sampling procedure. The concentrations were adjusted to 1 mg/hour of oxycodone hydrochloride infusion rate. The plots indicate the observed concentration of oxycodone and are marked by intravenous (IV) infusion and subcutaneous (SC) infusion, separately. (a) 0 to 96 hours after constant infusion, (b) 0 to 12 hours after constant intravenous infusion, and (c) 0 to 12 hours after constant subcutaneous infusion. Sampling time at steady state was treated as 96 hours after constant infusion.

the mean and its standard error of the final parameter, for each parameter.

Observed plasma oxycodone concentration data were also compared with the distribution of concentrations simulated by Monte-Carlo procedure from the final population pharmacokinetic model by visual inspection. The 10,000 concentration sets after constant intravenous infusion and constant subcutaneous infusion were simulated at the each time from the final model, respectively. BSA was re-sampled from the original data set. The median and 90% CI, which were obtained as the 500th and 9500th smallest values out of 10,000 simulated concentration sets from the final model, were superimposed and compared with the observed plasma oxycodone concentrations.

RESULTS

Noncompartmental Analysis

Plasma concentration profiles of oxycodone, noroxycodone, and oxymorphone after bolus intravenous administration, constant intravenous infusion, and constant subcutaneous infusion are described in (Figure 1). Pharmacokinetic parameters of oxycodone estimated by noncompartmental analysis from the plasma concentration profiles were summarized in (Tables 3 and 4). Elimination phase was not shown clearly in noroxycodone concentration profile after oxycodone bolus intravenous administration in the range of 0 to 6 hours as indicated in (Figure 1(a)). Oxymorphone concentrations were very low and less than 2% of oxycodone concentrations after oxycodone bolus intravenous administration and constant infusion. Plasma noroxycodone and oxymorphone concentrations at steady state were summarized in (Table 4).

Population Pharmacokinetic Analysis

A total of 234 plasma oxycodone concentrations in 89 patients with cancer pain after oxycodone infusion (69 patients after intravenous infusion and 20 patients after subcutaneous infusion) were included in population pharmacokinetic analysis. Plasma concentrations below the limit of quantification (<0.100 ng/mL) were not used for this analysis. Number of plasma concentration data per subject was summarized in (Table 1).

Based on the analysis for a base model, plasma concentrations of oxycodone were best described by one-compartment model and exponential error model was selected for intra-individual variability. The relationships between demographics of patients and Bayesian-estimated pharmacokinetic parameters (CL, V) based on the base model were examined. The CL related statistically to age, BWT, BSA, sex, and CLcr according to a change in OBJ of 3.84 at the significant level of 5% based on χ^2 test, while V did not relate statistically to age, BWT, and sex. The relationships between CL and significantly related demographic data were shown in (Figure 2). In the model building process to evaluate covariates, the effect of BSA on CL was found to be the most significant covariate ($p < 0.0005$, $\Delta OBJ = -13.507$, compared with the base model, the covariate model). Other covariates were not selected after inclusion of BSA.

Lag time (0.505 hour) was found to be significant for the constant subcutaneous infusion ($p < 0.0001$, $\Delta OBJ = -27.188$, compared with the covariate model). Pharmacokinetic difference between constant intravenous infusion and constant subcutaneous infusion was evaluated on the basis of the covariate model by adding the factor of administration route (intravenous infusion or subcutaneous infusion) as a fixed effect for CL, and V into the model. No difference was found in CL and V between intravenous infusion and subcutaneous infusion. Model building process was shown in (Table 5). Population pharmacokinetic parameters of the final model were shown in (Table 6).

Model Evaluation of the Final Population Pharmacokinetic Model

Scatter plots for observed concentration versus population mean predicted concentration and observed concentration versus Bayesian-estimated individual predicted concentration are also shown in (Figure 3). The diagnostic plots demonstrated that the final model adequately described the plasma concentrations, suggesting good fit of the final model to the data and a lack of bias. The stability and robustness of the final population pharmacokinetic model was evaluated using the nonparametric bootstrap procedure. The model was fitted repeatedly to 1000 bootstrap sample sets. Proportion of convergence in the fitting process was 99.5%. The median parameter estimates and 95% CIs obtained from the bootstrap sample sets are shown in Table 6 along with the parameter estimates in the final model. The population parameter estimates obtained from 1000 bootstrap sample sets were comparable to the estimates from the final models, indicating that the parameter estimates in the final models had little bias and the final model was fairly robust. Figure 4 shows the plots for the observed plasma concentration, and median and 90% CI profiles simulated by the Monte-Carlo procedure from the final model. The median and 90% CI profiles were consistent with the observed plasma concentration data after constant intravenous infusion and constant subcutaneous infusion.

DISCUSSION

In this report, we performed a noncompartmental analysis using the data from clinical studies which include nonsteady-state and steady-state plasma concentration profiles after intravenous bolus administration, constant intravenous infusion, and subcutaneous infusion in Japanese patients with cancer pain and developed the population pharmacokinetic model for oxycodone using the plasma oxycodone concentration data after constant intravenous and subcutaneous infusion.

TABLE 5. Model building process

Model No	Population model	OBJ	ΔOBJ	Model Compared	P-value
	Screening for covariate candidates				
1	Base model: $CL = \theta_1$, $V = \theta_2$	1266.820	–	–	–
2	$CL = \theta_1 \times (Age/67)^{\theta 2}$	1258.109	−8.711	1	<0.005
3	$CL = \theta_1 \times (BWT/51.7)^{\theta 2}$	1256.397	−10.423	1	<0.005
4	$CL = \theta_1 \times (BSA/1.53)^{\theta 2}$	1253.313	−13.507	1	<0.001
5	$CL = \theta_1 + \theta_2 \times Sex$	1257.317	−9.503	1	<0.005
6	$CL = \theta_1 \times (Scr/0.77)^{\theta 2}$	1266.767	−0.053	1	NS
7	$CL = \theta_1 \times (CLcr/65.5)^{\theta 2}$	1257.311	−9.509	1	<0.005
8	$CL = \theta_1 \times (AST/22)^{\theta 2}$	1265.230	−1.590	1	NS
9	$CL = \theta_1 \times (ALT/19)^{\theta 2}$	1266.796	−0.024	1	NS
10	$V = \theta_2 \times (Age/67)^{\theta 3}$	1266.716	−0.104	1	NS
11	$V = \theta_2 \times (BWT/51.7)^{\theta 3}$	1264.109	−2.711	1	NS
12	$V = \theta_2 + \theta_3 \times Sex$	1265.895	−0.925	1	NS
	Covariate model building by forward selection and backward elimination procedures				
13	$CL = \theta_1 \times (BSA/1.53)^{\theta 2} \times (BWT/51.7)^{\theta 3}$	1251.834	−1,479	4	NS
14	$CL = \theta_1 \times (BSA/1.53)^{\theta 2} \times (CLcr/65.5)^{\theta 3}$	1251.455	−1.858	4	NS
15	$CL = \theta_1 \times (BSA/1.53)^{\theta 2} \times (Age/67)^{\theta 3}$	1248.639	−4.674	4	<0.05
16	$CL = \theta_1 \times (BSA/1.53)^{\theta 2} \times (1 + \theta_3 \times Sex)$	1252.117	−1.196	4	NS
	Evaluation of PK difference between intravenous infusion and subcutaneous infusion for final model building				
17	$CL = \theta_1 \times (BSA/1.53)^{\theta 2}$, $V = \theta_3$ Lag time = 0 (IV infusion), θ_4 (SC infusion)	1226,125	−27.188	4	<0.001
18	Exclude inter-individual variability for lag time	1240.203	14.078	17	<0.001
19	$CL = \theta_1 \times (BSA/1.53)^{\theta 2} \times (1 + \theta_3 \times$ Administration Route)	1223.730	−2.395	17	NS
20	$V = \theta_3 \times (1 + \theta_4 \times$ Administration Route)	1226.033	−0.092	17	NS

OBJ: objective function value, ΔOBJ: change in objective function value, NS: not significant, BWT: body weight, BSA: body surface area, Scr: serum creatinine, CLcr: estimated creatinine clearance, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Sex: 0 for male, 1 for female, Administration Route: 0 for IV infusion, 1 for SC administration

TABLE 6. Parameter estimates for the final population pharmacokinetic model with the results of 1000 bootstrapped runs

Final pharmacokinetic model
CL (L/hour) = $\theta_1 \times (BSA/1.53)^{\theta 2}$
V (L) = θ_3
Lag time (hour) = 0 (intravenous infusion), θ_4 (subcutaneous infusion)

	Final parameter estimate			Estimate from 1000 bootstrap sample sets		
Parameter	Population mean	95% CI		Median	95% CI	
θ_1	25.7	23.8	27.6	25.6	23.9	27.7
θ_2	1.18	0.488	1.87	1.20	0.502	1.91
θ_3	214	181	247	214	184	250
θ_4	0.505	0.231	0.779	0.518	0.239	0.791
ω_{CL} (CV%)	32.7	26.1	38.2	32.1	26.1	37.9
ω_V (CV%)	39.4	20.9	51.6	38.3	21.6	53.5
$\omega_{Lag\ time}$ (CV%)	81.7	24.8	113	78.2	0.837	132
σ (CV%)	16.6	13.6	19.2	16.6	13.5	19.3

BSA: body surface area (m^2), Success rate of convergence: 99.5%