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ORIGINAL ARTICLE

Target-controlled infusion and population pharmacokinetics of landiolol hydrochloride in gynecologic patients

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Abstract
Purpose We previously determined the pharmacokinetic (PK) parameters of landiolol in healthy male volunteers. In this study, we evaluated the usefulness of target-controlled infusion (TCI) of landiolol hydrochloride and determined PK parameters of landiolol in gynecologic patients.
Methods Nine patients who were scheduled to undergo gynecologic surgery were enrolled. After inducing anesthesia, landiolol hydrochloride was administered at the target plasma concentrations of 500 and 1,000 ng/mL for each 30 min. A total of 126 data points of plasma concentration were collected from the patients and used for the population PK analysis. Furthermore, a population PK model was developed using the nonlinear mixed-effect modeling software.
Results The patients had markedly decreased heart rates (HRs) at 2 min after the initiation of landiolol hydrochloride administration; however, their blood pressures did not markedly change from the baseline value. The concentration time course of landiolol was best described by a 2-compartment model with lag time. The estimate of PK parameters were total body clearance (CL) 34.0 mL/min/kg, distribution volume of the central compartment (V_1) 74.9 mL/kg, inter-compartmental clearance (Q) 70.9 mL/min/kg, distribution volume of the peripheral compartment (V_2) 38.9 mL/kg, and lag time (ALAG) 0.634 min. The predictive performance of this model was better than that of the previous model.
Conclusion TCI of landiolol hydrochloride is useful for controlling HR, and the PK parameters of landiolol in gynecologic patients were similar to those in healthy male volunteers and best described by a 2-compartment model with lag time.

Keywords Landiolol hydrochloride · Pharmacokinetics · Target-controlled infusion

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Introduction

Landiolol hydrochloride is a newly developed cardioselective, ultra-short-acting β_1-adrenergic receptor blocking agent and has been used in the emergency management of atrial fibrillation, atrial flutter, and tachycardia, as well as for perioperative arrhythmia control [1, 2]. Landiolol has a short half-life ($t_{1/2}$ = about 4 min) and high cardioselectivity ($\beta_1/\beta_2 = 255$). Since the dose–response relationship was already proven, the standard maintenance dose was

selected on the basis of the dose mentioned in the package insert (10–40 μg/kg/min). However, a lower dose of landiolol hydrochloride has been reported to be effective [3], suggesting a variation in the patients' sensitivity to the drug. However, whether the effectiveness of landiolol is attributable to its pharmacokinetics (PKs) or pharmacodynamics is still unknown because of a lack of information on the PK of landiolol in surgical patients. In our previous study, we have already identified the PK parameters of landiolol in healthy male volunteers [4]. Therefore, in order to address the above question, we planned to study the PK parameters of landiolol in surgical patients. Since the PK parameters of landiolol in healthy male volunteers made it possible for us to administer landiolol hydrochloride using a target-controlled infusion (TCI) system, we planned the present study with the purpose of verifying the TCI-based infusion of landiolol hydrochloride and determining the PK parameters of landiolol in gynecologic patients.

Methods

Clinical methodology

The study was approved and supervised by the Research Ethics Committee of Asahikawa Medical University and registered with UMIN clinical trial registry (UMIN000007034), and informed consent was obtained from each patient. Nine patients who were scheduled to undergo gynecologic surgery were enrolled in this study. The inclusion criteria for our study were age of between 18 and 80 years, weight of <80 kg, and an American Society of Anesthesiologists (ASA) physical status score of 1 or 2. Patients with arrhythmias, such as atrial fibrillation or disturbance of the conduction system, and who received α-methyldopa, clonidine, or beta-blockers were excluded from this study.

The patients were fasted from midnight before the study and received no premedication. On arrival at the study site, an 18-G intravenous cannula was used for administration of landiolol hydrochloride and a 20-G intravenous cannula for administration of other drugs; the cannulae were inserted at the forearm and the dorsum of the hand, respectively. After an initial 500-mL infusion of Ringer's acetate solution via both the catheters for 30 min, the solution was infused at a rate of 60 mL/h via the former catheter and 80 mL/h via the latter. A 20-G catheter was inserted into the radial artery to sample blood for analysis of plasma landiolol concentrations. A 19-G epidural catheter was inserted through the Th12–L1 intervertebral space. General anesthesia was induced and the TCI of propofol and fentanyl was maintained. Propofol was administered using Diprifusor (AstraZeneca Pharmaceuticals, Cheshire, UK), and the target concentration of propofol was adjusted to maintain the bispectral index (BIS) value (Aspect A2000 BIS Anesthesia Monitor; Nihon Kohden, Tokyo, Japan) of 40–60. Fentanyl was administered by the TCI system with a target effect-site concentration (ESC) of 2 ng/mL. The STANPUMP software (available at http://opentci.org/doku.php; accessed on December 1, 2011) was used to run the infusion pump (Graseby™ 3500 Syringe Pump; Smiths Medical, UK) with the Shafer parameter setting [5]. Vecuronium (1 mg/kg) was administered for intubation and additional 2-mg doses of vecuronium were administered every 30 min. Twenty minutes prior to the skin incision, 8 mL of ropivacaine (0.375 %) was administered into the epidural space, and a continuous infusion at 6 mL/h was maintained thereafter. After making the incision to the peritoneum, we ensured that the vitals remained stable and started TCI of landiolol hydrochloride by using a Harvard pump (Harvard Pump 22; Harvard Apparatus Co., South Natick, MA, USA), which was controlled by the STANPUMP software with Honda's parameter [4] of the 2-compartment model. Only landiolol was administrated via 18-G cannula with carrier water. The landiolol line was connected to the nearest port with an intravenous (IV) line to minimalize dead space. Since STANPUMP software cannot input lag time (ALAG), we used Honda's parameter without ALAG. Attention is needed to the fact that this method shifts the predicted plasma concentration curve parallel towards the left, although the administration strategy does not change and PK analysis was not affected because of the use of the actual history of administration of landiolol for PK analysis. TCI of landiolol hydrochloride was performed to achieve target plasma concentrations of 500 and 1,000 ng/mL (Fig. 1.). These concentrations were chosen to represent approximately 50 and 100 % of the concentration during the highest clinical dosage [1]. If the patients developed bradycardia (HR <45 beats/min [bpm]), 0.5 mg of atropine was intravenously administered. If bradycardia was not cured, administration of landiolol was stopped and the study was terminated. If the patient developed hypotension (systolic blood pressure [SBP] <80 mmHg or 20 % less than the baseline value) accompanied by slight bradycardia (HR <60 bpm), 5 mg of ephedrine was intravenously administered. In cases of hypotension without bradycardia (HR ≥60 bpm), 0.05 mg of phenylephrine was administered. To avoid affecting the pharmacodynamics of landiolol, care was taken not to administer any cardiovascular agent 5 min before and after changing the target concentration of landiolol.

Blood sampling and landiolol assay

During evaluation of the PK model by landiolol hydrochloride administration with a computer-controlled

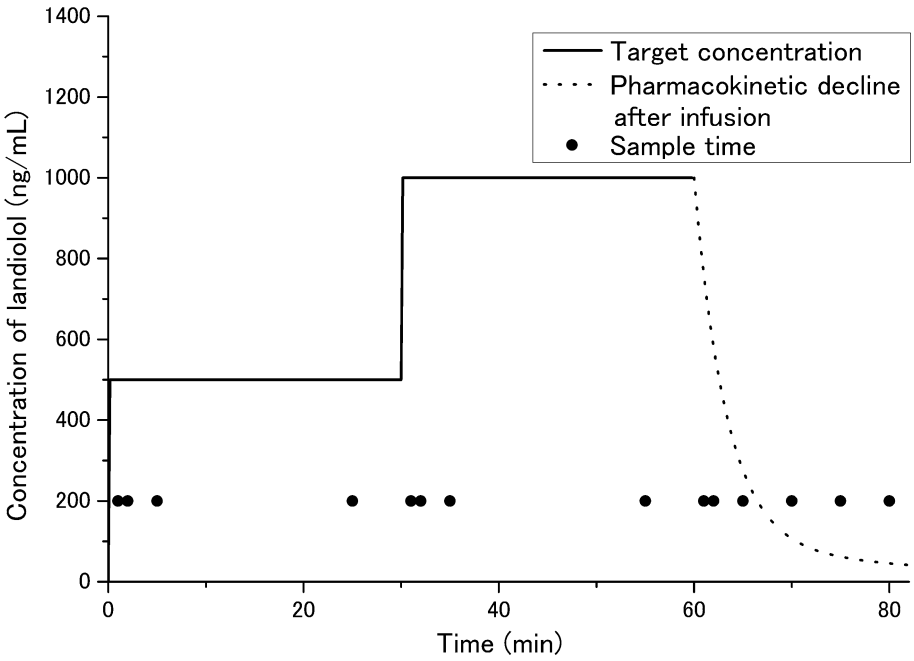

Fig. 1 Sample times, target concentration, and predicted concentrations after infusion using the target-controlled infusion (TCI) system according to the previous parameters in healthy males. The predict plasma concentration was shifted parallel towards the left for 0.820 min because ALAG was not used

infusion pump, concentrations were determined at 1, 2, 5, and 25 min after beginning infusion and after changing target concentration and at 1, 2, 5, 10, 15, and 20 min after termination of the infusion, as shown in Fig. 1. One milliliter of whole blood was collected in a test tube filled with chilled ethanol and neostigmine; the neostigmine was syringed in the presence of EDTA-2Na dust to prevent landiolol from being hydrolyzed by the pseudocholinesterase enzyme present in plasma. The plasma was collected after centrifugation at 1,600*g* for 10 min and stored at −20 °C until the landiolol concentration was assayed [6]. The plasma samples were assayed using a high-performance liquid chromatography method with fluorescence detection, as reported by Suno et al. [6].

PK and pharmacodynamic analysis

One-way analysis of variance (ANOVA) was performed for overall comparison of the hemodynamic values. If the values showed a significant difference, a post hoc analysis using the Tukey–Kramer test was performed to compare the baseline value and values obtained after administration of landiolol hydrochloride.

The population PK model was developed using the nonlinear mixed-effect modeling software (NONMEM, version V, level 1.1; GloboMax LLC, Hanover, MD, USA). First-order conditional estimation with the interaction method was used for parameter estimation. After investigation of 1-, 2-, and 3-compartment models, the concentration time course of landiolol was best described by a 2-compartment model. The model parameters were total body clearance (CL, mL/min/kg), distribution volume of the central compartment (V_1, mL/kg), inter-compartmental clearance (Q, mL/min/kg), distribution volume of the peripheral compartment (V_2, mL/kg), and lag time (ALAG, min). The inter-individual variability in the PK parameters of landiolol was investigated using an additive and exponential error model. Residual variability was also investigated using an additive, exponential, and mixed error model.

Starting from a simple compartment model, a variety of covariates that could influence the PK of landiolol were added in a stepwise manner to the basic model (forward selection method). An individual covariate was considered to improve the model significantly if the difference in the objective function value (ΔOBJ) between the basic model and the tested model was >3.84 ($p < 0.05$). Covariates considered for inclusion in the model were subject demographic factors (body weight, lean body mass [7], and age). The influence of these covariates was treated as a continuous function. In order to confirm that the final model actually reflects the observed plasma concentrations, the predicted values were plotted against the observed values for the final model, and the conditional weighted residuals [8] were plotted against the predicted values or the time after beginning of infusion. The adequacy of the present model was evaluated by a visual predictive check. The visual predictive check was generated using 1,000 simulations from the present model and its parameter estimates including the inter-individual and residual variability. A graphical comparison was made between observed concentrations and the model predicted median and the 5th and 95th percentile

prediction interval over time. The percent performance error [(measured − predicted/predicted) × 100] for each concentration was also determined. The median performance error (MDPE), the median absolute performance error (MDAPE), and their 25th and 75th percentiles were determined. The MDPE and MDAPE represent the median bias of the model and the median accuracy of the prediction, respectively. These values for the previous and the present models were compared [9].

Results

Demographic information regarding the 9 gynecologic patients included in this study is shown in Table 1. The average age of the patients was 55 years (range 37–71 years), and the average weight was 62.8 kg (range 47.1–73.0 kg). A total of 126 data points of plasma concentration were collected from the patients and used for the population PK analysis. The observed concentrations in each point are shown in Fig. 2. In the steady state, the observed values were comparable to the concentrations predicted in the previous model, but the observed values showed a tendency to exceed the predicted values [4]. The predicted values from the following model were closer to the observed values, especially immediately after the target concentration was increased. Hemodynamic values are shown in Fig. 3. HR significantly decreased 2 min after starting the administration of landiolol hydrochloride and remained lower than the baseline HR until 20 min after the administration of landiolol hydrochloride ended. The BP value was also low; however, there was no significant change between the BP values at any particular time point and the basic value. None of the patients required administration of atropine. The amounts of ephedrine and phenylephrine administered were 8.9 ± 10.8 mg (range 0–30) and 0.21 ± 0.15 mg (range 0–0.45), respectively.

Table 1 Demographics and baseline clinical characteristics of the study patients

Baseline characteristics	Median or *n*	Range
Gender (male/female)	0/9	–
Body weight (kg)	62.8	47.1–73.0
Lean body mass (kg)	43.1	34.6–47.0
Age (years)	55	37–71
Albumin level (g/dL)	4.2	3.6–4.3
AST level (IU/L)	20	10–40
ALT level (IU/L)	17	7–49
Total bilirubin level (mg/dL)	0.6	0.5–0.8
Choline esterase level (IU/L)	303	272–338
BUN level (mg/dL)	12	8–19
Serum creatinine level (mg/dL)	0.55	0.36–0.67
Creatinine clearance (mL/min)	111	87.4–166

Creatinine clearance was calculated using the Cockcroft and Galt equation [17]

AST aspartate transaminase, *ALT* alanine transaminase, *BUN* blood urea nitrogen

The results of the population PK analysis suggest that the concentration time course of landiolol is best described by a 2-compartment model with lag time based on the Akaike Information Criterion (AIC) and diagnostic plots. The lag time is a necessary component in each model, because its incorporation significantly improved the plot fitting. The AIC values of 1- and 2-compartment models with lag time were 1382.897 and 1381.442, respectively. A 3-compartment model did not converge; thus, the 2-compartment model was used as the structural model. Next, random variables for inter-individual variability were added in a stepwise manner to develop the population model. No significant covariate was identified. For laboratory parameters (routine hematology and blood chemistry), the most of the values were within normal range except mildly abnormal total albumin, alanine aminotransferase, and serum creatinine levels shown in 1 out of 9 subjects. Since the frequency and extent of abnormality were limited, the laboratory parameters were not considered as covariates when constructing the model. Random variables for inter-individual variability were required for the parameters CL and V_1 as an exponential error model, but not for the Q, V_2, and ALAG parameters. Residual variability was best described by an exponential error model.

Table 2 shows the parameter estimates for the final model. The final parameters were CL 34.0 mL/min/kg, V_1 74.9 mL/kg, Q 70.9 mL/min/kg, V_2 38.9 mL/kg, and ALAG 0.634 min. The inter-individual variability in CL and V_1 was 6.3 and 6.6 %, respectively. The residual variability was 38.1 %. The predicted values by the present model were plotted against the observed values (Fig. 4). The scatters were symmetrically distributed on both sides, and we observed no significant bias. Conditional weighted residual plots are shown in Fig. 5. The plots were relatively symmetrical and mostly distributed around zero. No obvious bias pattern was observed in the plots of the conditional weighted residuals versus the predicted concentrations or the time after beginning of infusion. Figure 6 shows the 5th and 95th percentiles as well as the median from the visual predictive check simulation with the observed concentrations. This plot shows that most of the observed concentrations fell within the 5th–95th percentile prediction interval and observed concentrations <10 % lay outside the prediction intervals. The visual predictive check shows that the present model adequately describes the majority of the observed concentrations. We also

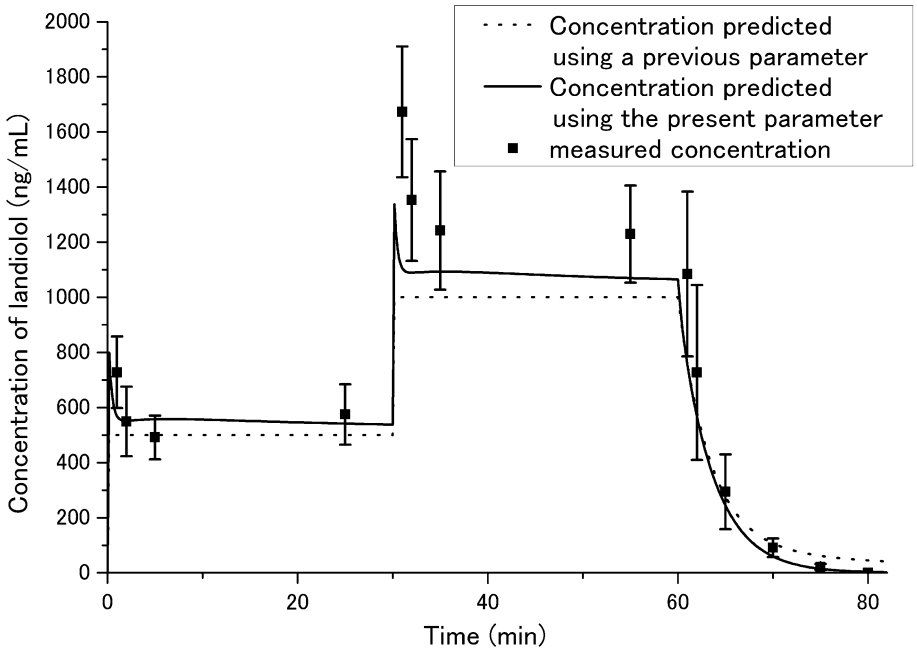

Fig. 2 Observed and predicted concentrations of landiolol. *Dashed line* shows the concentrations predicted using the previous parameters, and the *solid line* shows the concentrations predicted using the present parameters. The predict plasma concentration was shifted parallel towards the left for 0.820 min because ALAG was not used. Data are expressed as mean ± SD

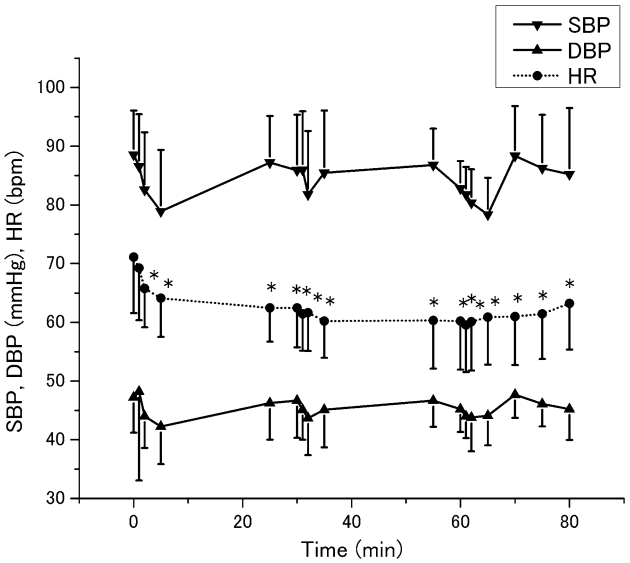

Fig. 3 Hemodynamic values. SBP, DBP, and HR are shown during and 20 min after administration of landiolol hydrochloride. In comparison with the baseline values, the SBP and DBP values after administration did not change significantly. The HR significantly decreased 2 min after starting administration of landiolol hydrochloride. Data are expressed as mean ± SD. *$p < 0.05$ when compared with the base value (0 min). *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *bpm* beats per minute

Table 2 Pharmacokinetic parameter estimates of landiolol from the population model

Fixed effect	Estimates of the model parameters	
	Healthy male volunteers [4] Mean ± SE	Gynecologic patients Mean ± SE
TVCL (mL/min/kg)	36.6 ± 1.23	34.0 ± 1.96
TVV_1 (mL/kg)	101 ± 8.83	74.9 ± 13.2
TVQ (mL/min/kg)	16.1 ± 3.70	70.9 ± 68.9
TVV_2 (mL/kg)	55.6 ± 6.05	38.9 ± 9.03
TVALAG (min)	0.820 ± 0.0613	0.634 ± 0.00115
	Mean ± SE (CV %)	Mean ± SE (CV %)
Inter-individual variability		
ω^2_{CL}	0.0475 ± 0.00874 (21.8)	0.00400 ± 0.00239 (6.3)
ω^2_{V1}	0.214 ± 0.0426 (46.3)	0.00434 ± 0.0201 (6.6)
Residual variability		
σ^2	0.0490 ± 0.00757 (22.1)	0.145 ± 0.0134 (38.1)

TVCL typical value of total body clearance, TVV_1 typical value of the distribution volume of the central compartment, *TVQ* typical value of the inter-compartment clearance, TVV_2 typical value of the distribution volume of the peripheral compartment, *TVALAG* typical value of the lag time, ω^2_{CL} inter-individual variability in CL, ω^2_{V1} inter-individual variability in V_1, σ^2 residual variability, *CL* total body clearance, V_1 distribution volume of the central compartment

plotted a comparison of the performance errors in the previous model and the present models (Fig. 7). The MDPE values of the previous and present models were 16.0 (−11.4, 43.1) and 7.8 (−9.5, 25.8), respectively (Table 3). The MDAPE of the present model was 19.7 (8.9, 32.0) and outweighed that of the previous model (30.9 [15.1, 48.2]). The predictive performance of the present model was better than that of the previous model. In addition, the MDPE of the present model was between −20 and 20 %, and MDAPE was <30 %. These values met the

acceptable criteria of model performance defined by Glass et al. [10].

Discussion

Low-dose administration of landiolol hydrochloride has been reported to be useful for the prevention of ischemic heart disease and atrial fibrillation for high-risk patients in the intensive care unit [3], thereby suggesting that poor-risk patients have a higher sensitivity and lower dose requirement of landiolol hydrochloride. However, the report did not attribute this finding to the PK or pharmacodynamics. In this study, we fitted a 2-compartment model in a finding consistent with that of the previous study and showed that there were no major differences in the PK of landiolol between healthy male volunteers and anesthetized female patients. The present study was intended to be an intermediate study between studies on landiolol requirement in healthy males and landiolol requirement in patients with cardiothoracic disease and/or elderly patients who are at a high risk for cardiovascular disease and require beta-blockers; therefore, further studies are required to determine the PK parameters of landiolol in these patients.

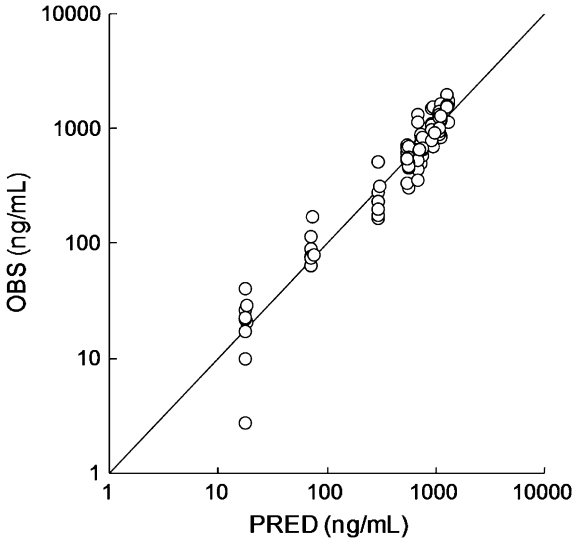

Fig. 4 Observed concentrations versus predicted concentrations from the present model. The *solid line* represents the unit line. *OBS* observed concentrations, *PRED* predicted concentrations

It has been established that PK simulation and TCI are useful for anesthetic administration [11–13], and cardiovascular agents are considered to be similar to anesthetics [14]. We tried to administer landiolol hydrochloride using the TCI system to test the PK parameters of healthy volunteers. Although the PK parameters of the healthy volunteers were used, we noted that the observed experimental values were reasonably close to the predicted values; hence, we found the landiolol hydrochloride TCI was useful. However, although PK parameters were acquired in the previous study and in this study during normal sinus rhythm, PK parameters may change in a clinical setting. Attention was needed for adjustment of target concentration when TCI of landiolol was used in a clinical setting. Moreover, since the PK values obtained in the present study improved the precision with which plasma concentration of landiolol could be predicted, the accuracy of TCI was expected to increase after the modification of the PK

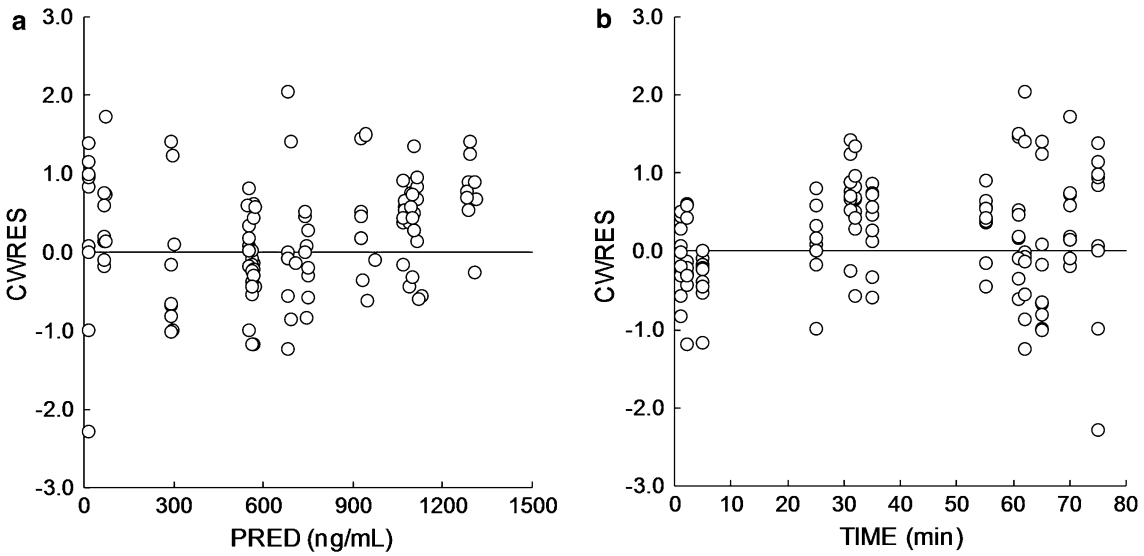

Fig. 5 Diagnostic plots of conditional weighted residuals versus predicted concentrations (**a**) or time after beginning of infusion (**b**). The *horizontal line* represents the zero level. *CWRES* conditional weighted residuals, *PRED* predicted concentrations

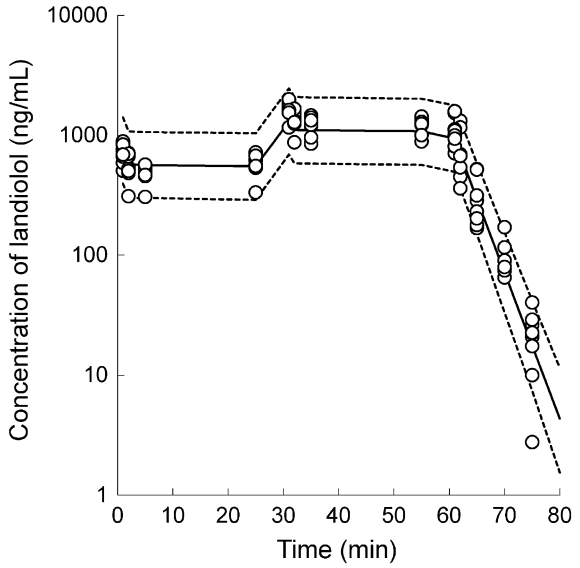

Fig. 6 Visual predictive check of the present model. *Open circles* represent the observed concentration. The *solid line* represents the median of the prediction interval. *Dotted lines* represent the 5th and 95th percentile prediction intervals

parameters that are influenced by gender, age, and concomitant use of drugs, including anesthetics. These effects, however, were limited because landiolol is predominantly metabolized by the pseudocholinesterase, which is abundant in plasma [15]. Since the concentration of landiolol is subject to change as a result of the continuous infusion dose because of its rapid action and ease of titration, the merit of TCI is not as large as it is for long-acting anesthetics. However, similar to remifentanil, a short-acting drug metabolized by esterase, TCI of landiolol may have some merits, such as ease of administration on the basis of concentration, thereby preventing unnecessary overdosing, as might occur with continuous infusion [12].

With regard to the hemodynamics, the patients showed low BP throughout the study and a pressor was required; however, landiolol did not significantly affect BP. The main reason for low BP and the necessity of a pressor was sufficient anesthesia, such as epidural anesthesia or TCI of fentanyl to prevent hemodynamics from being affected by surgical stimuli. The HR significantly decreased after the initial administration of landiolol hydrochloride and remained constant throughout the study. This finding confirmed that landiolol could safely be used for patients with normal HR and that TCI was a useful and a safe option for landiolol administration in these patients, despite the temporary increase in the concentration of landiolol.

The plasma concentrations predicted from the previous model led to an underestimation of the plasma concentrations in gynecologic patients. One of the reasons for underestimation might have been the difference in the distribution volume. The V_1 in the present study was lower than that in the previous study (101 ± 8.83 vs

Table 3 Comparison of prediction performance between the previous and present model

	MDPE	MDAPE
Previous model	16.0 (–11.4, 43.1)	30.9 (15.1, 48.2)
Present model	7.8 (–9.5, 25.8)	19.7 (8.9, 32.0)

Data are expressed as median (25th, 75th percentiles)

MDPE median performance error, *MDAPE* median absolute performance error

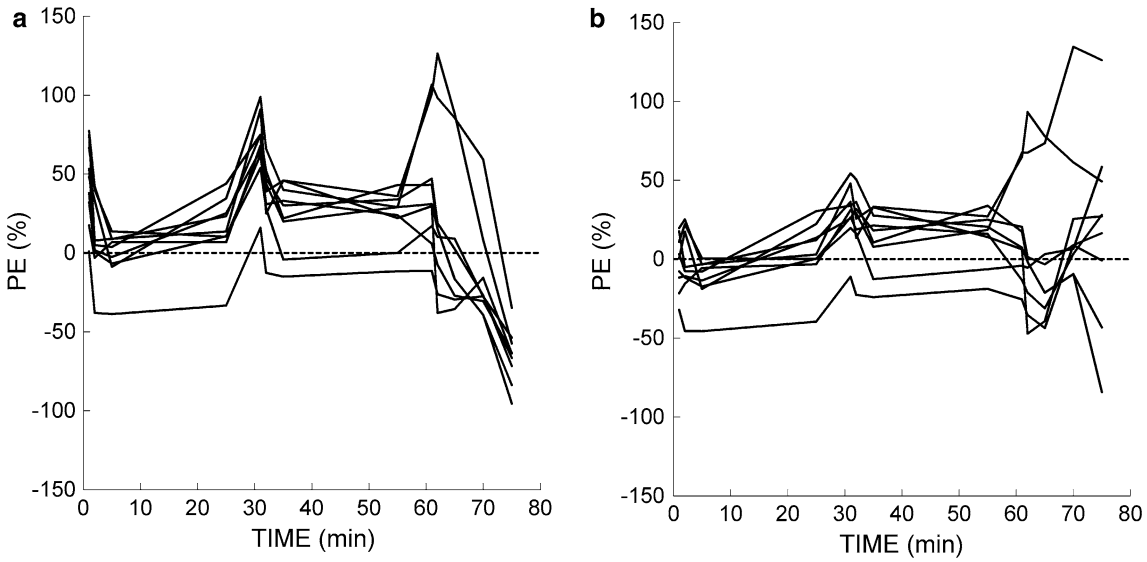

Fig. 7 Percent performance errors versus time after beginning of infusion. PE in the left (**a**) and right (**b**) figure was calculated using the previous and present model, respectively. The *horizontal line* represents the zero level. *PE* performance errors

74.9 ± 13.2 mL/kg). Another reason for underestimation might be the CL difference between healthy volunteers and gynecologic patients, since the clearance of esmolol in anesthetized patients has been reported to be lower than that in unanesthetized healthy male volunteers [16]. However, the clearance values obtained for healthy volunteers and gynecology patients were similar (36.6 ± 1.23 vs 34.0 ± 1.96 mL/min/kg). Thus, the new model provided an improved fit for the observed concentrations; however, the predicted concentrations for the target concentration of 1,000 ng/mL were lower. This finding might be attributable to the fact that landiolol has a slightly nonlinear PK profile, which could be a limitation of the model. Moreover, since the indication of landiolol is controlling HR for tachycardia, the PKs may change in a clinical setting. This is limitation of this study, and further study may be needed for to reveal PK parameters for patients with tachycardia.

Conclusion

In summary, the PK of landiolol is best described by a 2-compartment model. The PK parameter values of landiolol obtained for healthy male volunteers presented a good prospective performance when tested using the TCI method. The PK parameter values obtained for gynecologic patients were similar to the corresponding values obtained for healthy male volunteers.

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Conflict of interest Takayuki Kunisawa received a speaker's honorarium from Ono Pharmaceutical Co., Ltd., (Osaka, Japan) for delivering a lecture on landiolol; the contents of the present study were not included in the lecture. Takayuki Kunisawa received a speaker's honorarium from AstraZeneca K.K. (Osaka, Japan) for delivering a lecture on propofol; the contents of the present study were not included in the lecture. Takayuki Kunisawa received research grants from AstraZeneca K.K. (Osaka, Japan) for scientific research on PK simulation; however, these grants were not used for this study. Susumu Nakade and Ryunosuke Higashi, who conducted population PK analysis using fixed data supplied by Asahikawa Medical University, are employees of Ono Pharmaceutical Co., Ltd., (Osaka, Japan), which sells landiolol hydrochloride in Japan.

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