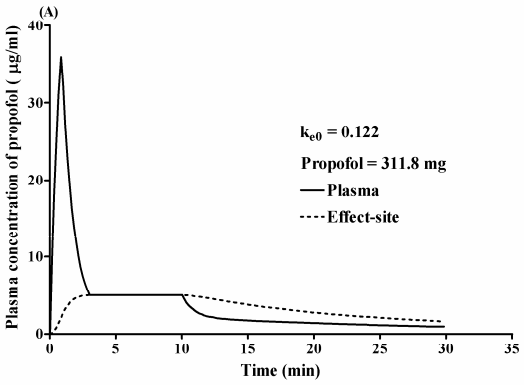
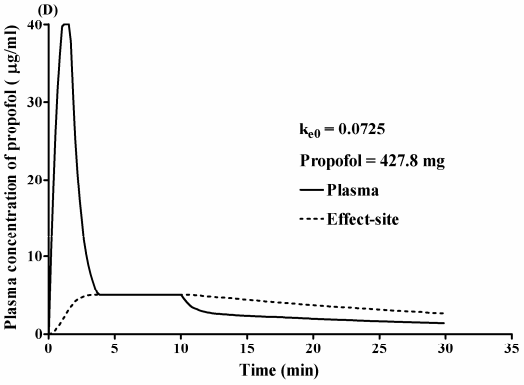
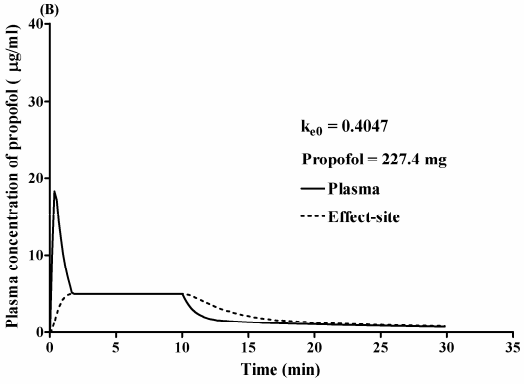
Adjustment of k_{e0} to Reflect True Time Course of Drug Effect by Using Observed Time to Lowest BIS after an Intravenous Bolus and an Adaptation of the Time-to-peak-effect Algorithm Reported by Shafer and Gregg.[1]

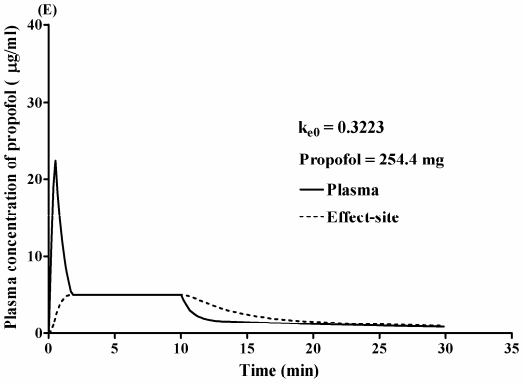
Using observed time to lowest BIS after an intravenous bolus, designated as t_{peak}, and an adaptation of the time-to-peak-effect algorithm reported by Shafer and Gregg,[1] we adjusted k_{e0} and simulated effect-site target-controlled infusion with the target of 5.0 μg/ml for 10 min for both the unadjusted and adjusted k_{e0} values (Asan Pump, version 1.3, Bionet Co., Ltd., Seoul, Korea).

Time to lowest BIS after an intravenous bolus was 1.5 ± 0.9 (mean ± SD) min for lipid emulsion and microemulsion propofol. The k_{e0} was adjusted to produce peak effect on the BIS at 1.5 minute after an intravenous bolus for both formulations. With unadjusted k_{e0}, the cumulative dose of propofol and the overshoot of the calculated plasma concentration of propofol were much higher than those with adjusted k_{e0} on the basis of the observed t_{peak} (fig. 1). For lipid emulsion formulation, a simulation with adjusted k_{e0} resulted in a close similarity of the cumulative dose of propofol and the height of overshoot to those in Schnider model (fig. 1).[2]


(A)
Plasma concentration of propofol (µg/ml)
Time (min)
k_{e0} = 0.122
Propofol = 311.8 mg
Plasma
Effect-site


(D)
Plasma concentration of propofol (µg/ml)
Time (min)
k_{e0} = 0.0725
Propofol = 427.8 mg
Plasma
Effect-site


(B)
Plasma concentration of propofol (µg/ml)
Time (min)
k_{e0} = 0.4047
Propofol = 227.4 mg
Plasma
Effect-site


(E)
Plasma concentration of propofol (µg/ml)
Time (min)
k_{e0} = 0.3223
Propofol = 254.4 mg
Plasma
Effect-site

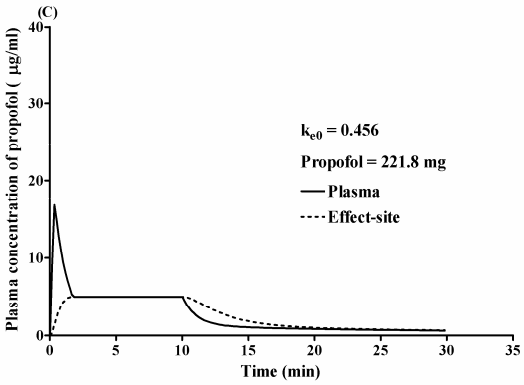

(C)
Plasma concentraion of propofol (µg/ml)
Time (min)
k_{e0} = 0.456
Propofol = 221.8 mg
Plasma
Effect-site

Figure 1. Simulated effect-site target-controlled infusion of lipid emulsion and microemulsion propofol with the target of 5.0 μg/ml for 10 minutes in a subject whose age, body weight, and height are 44 yr old, 65 kg and 170 cm (Asan Pump, version 1.3, Bionet Co., Ltd., Seoul, Korea). (A) with unadjusted k_{e0} for lipid emulsion formulation, (B) with adjusted k_{e0} on the basis of an adaptation of the time-to-peak-effect algorithm for lipid emulsion formulation (t_{peak} = 1.5 minutes), (C) with Schnider model (k_{e0} = 0.459 min^{-1}) for lipid emulsion formulation, (D) with unadjusted k_{e0} for microemulsion, (E) with adjusted k_{e0} on the basis of an adaptation of the time-to-peak-effect algorithm for microemulsion formulation (t_{peak} = 1.5 minutes). t_{peak}: time to lowest bispectral index after an intravenous bolus of lipid emulsion and microemulsion 2 mg/kg as propofol.

Using infusion-only data and bispectral index, Doufas et al.[3] and Billard et al.[4] reported k_{e0} to be 0.17 $min^{-1}$and 0.20 min^{-1}, respectively. The estimate of k_{e0} of lipid emulsion was 0.122 in this study using bolus plus infusion data and bispectral index. In all of these studies, BIS smoothing rate was set at 15 seconds. In contrast, in the study by Schnider et al., k_{e0} was 0.459 min^{-1} when it was obtained from bolus plus infusion data and canonical univariate parameter calculated every 2 seconds.[5] From these finding, it is speculated that the estimates of k_{e0}, obtained from relatively insensitive bispectral index (15 seconds of time delay),[3,4] are consistently smaller than that from relatively sensitive electroencephalographic measures (2 seconds of time delay).[5] If a bolus dose of propofol had influenced the electroencephalographic hysteresis in this study (bolus plus infusion data), the estimates of k_{e0} should have been larger than those from infusion-only data.[3,5] However, the time delay in bispectral index (15 seconds of smoothing rate) soundly explains the discrepancy of k_{e0} between sensitive (less time delay) and less sensitive surrogate measures of propofol effect: the more sensitive the electroencephalographic measures, the larger the k_{e0}. The apparently slow blood-brain equilibration rate of both formulations in this study, which might be caused by using relatively insensitive bispectral index as a surrogate measure of propofol effect, was successfully adjusted to reflect true time course of drug effect by using observed time to

lowest BIS after an intravenous bolus and an adaptation of the time-to-peak-effect algorithm reported by Shafer and Gregg.[1]

A simulation of zero-order infusion using pharmacokinetic parameters of lipid emulsion in this study (from bolus plus infusion data) showed a nearly identical predicted plasma concentration profile to that of Schnider model (from infusion data) (fig. 2A and B, solid lines).[2] This suggests that a pharmacokinetic model derived from bolus plus infusion data, like this study, perform as well as an infusion-only pharmacokinetic model does. Therefore, the estimates of k_{e0} in this study are not likely to be biased due to inaccurate description of pharmacokinetic behavior of the drugs.

The rate and extent of change in the effect-site concentration of propofol, simulated with k_{e0} and pharmacokinetic parameters of Doufas et al.[3] and with those for lipid emulsion in this study, are slower and less than those of Schnider model,[2,5] respectively (fig. 2A and C, dotted lines). After k_{e0} adjustment using observed t_{peak}, the effect-site concentration profile (fig. 2A, circle) of lipid emulsion in this study is nearly identical to that of Schnider model(fig. 2B, dotted line).[2,5] With k_{e0}, reported by Doufas et al.,[3] adjusted using t_{peak} of lipid emulsion in this study, the effect-site concentration profile was also improved (fig. 2C, circle).

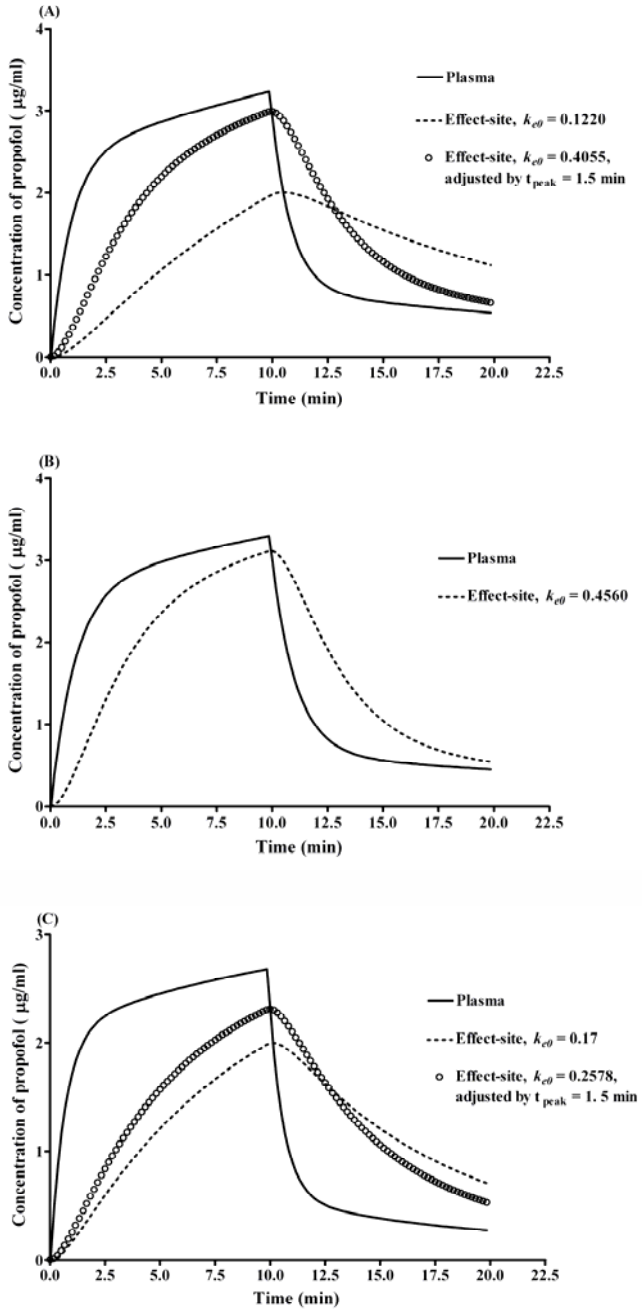


Figure 2. Simulated zero-order infusion of lipid emulsion propofol with the rate of 10 mg/kg/h for 10 minutes in a male subject whose age, body weight, and height are 44 yr old, 65 kg and 170 cm (Asan Pump, version 1.3, Bionet Co., Ltd., Seoul, Korea). (A) plasma concentration (solid line), effect-site concentration with unadjusted k_{e0} (dotted

line) and effect-site concentration (circle) with adjusted k_{e0} on the basis of an adaptation of the time-to-peak-effect algorithm (t_{peak} = 1.5 minutes) in this study, (B) plasma concentration (solid line) and effect-site concentration (dotted line) in Schnider model (k_{e0} = 0.459 min^{-1}), (C) plasma concentration (solid line) and effect-site concentration with unadjusted k_{e0} (dotted line) and effect-site concentration (circle) with adjusted k_{e0} on the basis of an adaptation of the time-to-peak-effect algorithm (t_{peak} = 1.5 minutes) in Doufas model.

t_{peak}: time to lowest bispectral index after an intravenous bolus of lipid emulsion 2 mg/kg as propofol in this study.

Assessment of Hemodynamic Effects of Lipid Emulsion and Microemulsion Propofol by Population Approach

The hemodynamic effects were described using an effect compartment model. The relationship of systolic blood pressure (SBP) with propofol effect-site concentration was analyzed using a sigmoid E_{max} model:[6]

$$Effect = E_0 + (E_0 - E_{\max})\frac{Ce^{\gamma}}{Ce_{50}{}^{\gamma} + Ce^{\gamma}} \qquad \text{equation - 1}$$

,where Effect is measured SBP, E_0 is the baseline SBP when no drug is present, E_{max} is the maximally decreased SBP, *Ce* is the calculated effect-site concentration of propofol, Ce_{50} is the effect-site concentration associated with 50% maximal decrease of SBP, and γ is the steepness of the concentration-versus-response relation.

Inter-individual random variability was modeled using log-normal model. No inter-individual variability of γ was assumed. Residual random variability was modeled using an additive error model.

Population pharmacodynamic parameter estimates and inter-individual variability of lipid emulsion and microemulsion of propofol for systolic blood pressure, including their non-parametric bootstrap replicates are found in table 1 and 2, respectively. The

$t_{1/2}k_{e0}$ for BIS was 5.68 minute for lipid emulsion. For microemulsion, it was 9.56 minutes for male and 4.15 minutes for female. The $t_{1/2}k_{e0}$ for systolic blood pressure was 7.95 minutes for lipid emulsion and 10.52 minutes for microemulsion. And therefore, for both formulations, the effect of propofol on the BIS occurs more rapidly than its effect on systolic blood pressure, which is the same finding as reported previously.[7]

For microemulsion formulation, age was a significant covariate for Ce_{50}, which is described by the following equation:

$$Ce_{50}\ (\mu g/ml) = 3.02 - 0.0261 \times (age - 44) \qquad \text{equation - 2}$$

Objective function value was decreased by 29.171 ($P < 0.0001$), compared with the basic model. With increasing age from 19 to 79 yr, Ce_{50} decreased by 42.6%.

The relationship between SBP and the effect-site concentration of propofol for lipid emulsion and microemulsion formulation and the change of observed, predicted and individually predicted SBP over time in volunteer ID 12 are shown in figure 3 and 4, respectively.

Kazama et al. reported that the effect of propofol on BIS occurs more rapidly than its effect on SBP and SBP decreases to a greater degree but more slowly with increasing age, which were the findings at pseudo-steady state condition.[7] In this study performed at non-steady state condition, the effect of propofol on the BIS occurs more rapidly than

its effect on systolic blood pressure, regardless of formulations. Age effect on SBP for lipid emulsion was not observed, while the sensitivity to microemulsion measured by the effect-site concentration associated with 50% maximal decrease of SBP (Ce_{50}) was decreased with increasing age. Kazama et al. assumed that hypotension in the elderly patients younger than 69 yr is mainly a result of pharmacokinetic changes, and that hypotension in patients older than 70 yr is a result of pharmacodynamic changes in addition to pharmacokinetic changes.[7] However, propofol plasma concentration at non-steady state condition is affected mainly by distribution rather than by metabolic clearance. Therefore, SBP change caused by metabolic clearance may not be observed at non-steady state condition, which may explain why we could not observe age effect on SBP in lipid emulsion.

Table 1. Population Pharmacodynamic Parameter Estimates (Standard Error, SE) and Inter-individual Variability (%CV) of Lipid Emulsion of Propofol for Systolic Blood Pressure

Parameters	Estimates (median, 2.5 - 97.5%)*	SE	%CV
k_{e0} (min^{-1})	0.0872 (0.087, 0.03 - 0.15)	0.00336	49.8
Ce_{50} (μg/ml)	3.27 (3.45, 0.6 - 5.73)	0.234	123.7
E_0	142 (138, 100 - 184)	3.4	13.8
E_{max}	81.6 (85, 50 - 110)	25.2	152.3
γ	3.13 (2.34, 0.5 - 3.6)	0.194	206.9
$\sigma^{2\dagger}$	41.5 (30.1 - 60.6)	4.43	–

*: median parameter values (2.5 - 97.5 percentiles) of the non-parametric bootstrap replicates.

Inter-individual random variability was modeled using log-normal model.

†: residual random variability was modeled using additive error model.

Table 2. Population Pharmacodynamic Parameter Estimates (Standard Error, SE) and Inter-individual Variability (%CV) of Microemulsion of Propofol for Systolic Blood Pressure

Model	Parameters	Estimates (median, 2.5 - 97.5%)*	SE	%CV
Basic	k_{e0} (min^{-1})	0.0699	0.00711	69.3
	Ce_{50} (μg/ml)	2.74	0.35	148.3
	E_0	140	4.67	17.3
	E_{max}	93.4	11.5	51.6
	$\gamma^{\dagger}$	1.96	0.152	–
	$\sigma^{2\ddagger}$	59.9	9.6	–

Final	k_{e0} (min^{-1})		0.0659 (0.0629, 0.05 - 0.0865)	0.0084	66.6
	Ce_{50} (μg/ml) = θ_1 - θ_2 × (age - 44)	θ_1	3.02 (2.67, 2.01 - 3.77)	0.432	127.7
		θ_2	0.0261 (0.0239, 0.01 - 0.0522)	0.0101	
	E_0		139 (138, 128 - 146)	4.64	17.8
	E_{max}		91.4 (91.2, 50 - 100)	12.4	51.2
	$\gamma^{\dagger}$		2.08 (2.23, 1.51 - 2.72)	0.197	–
	$\sigma^{2\ddagger}$		59.6 (60.6, 40.5 - 87.5)	9.53	–

*: median parameter values (2.5 - 97.5 percentiles) of the non-parametric bootstrap replicates.

†: no inter-individual random variability was assumed, inter-individual random variability of other structural model parameters was modeled using log-normal model.

‡: residual random variability was modeled using additive error model.

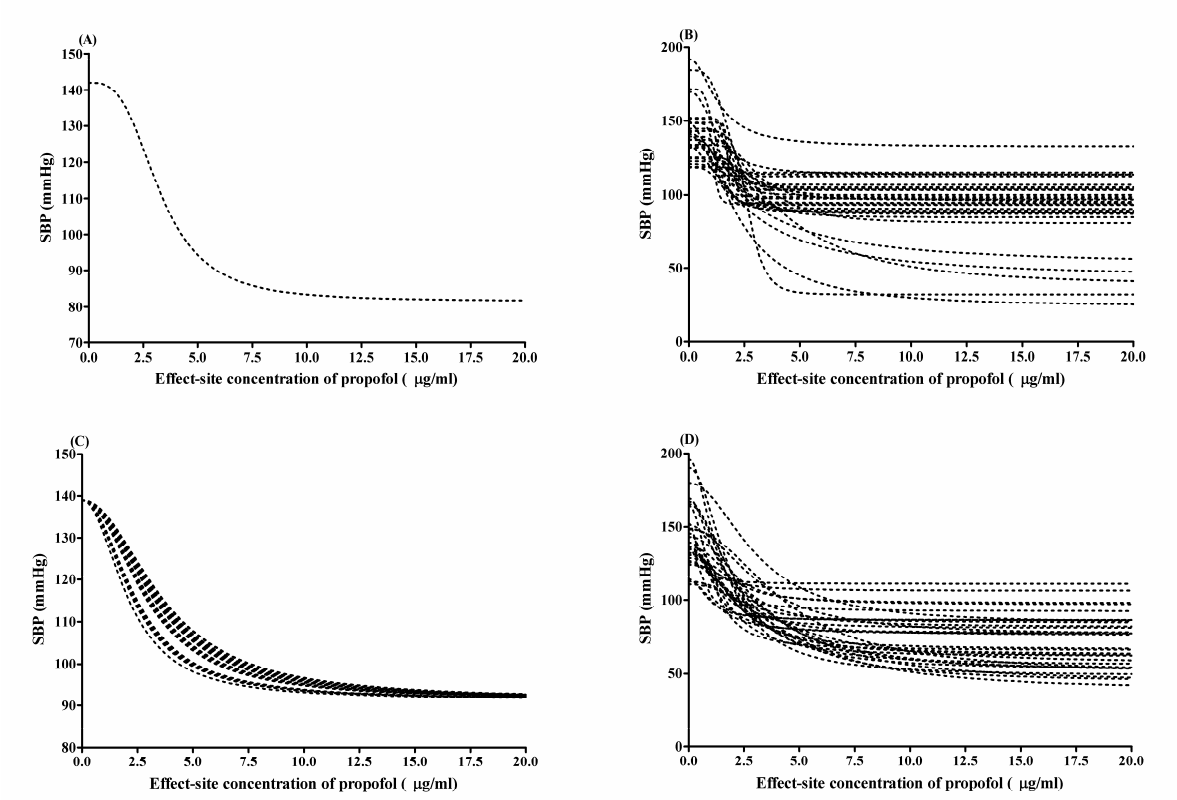


Figure 3. The relationship between systolic blood pressure (SBP) and the effect-site concentration of propofol for lipid emulsion and microemulsion formulation. (A) predicted SBP versus the effect-site concentration of propofol for lipid emulsion formulation, (B) individually predicted SBP versus the effect-site concentration of propofol for lipid emulsion formulation, (C) predicted SBP versus the effect-site concentration of propofol for microemulsion formulation, (D) individually predicted SBP versus the effect-site concentration of propofol for microemulsion formulation.

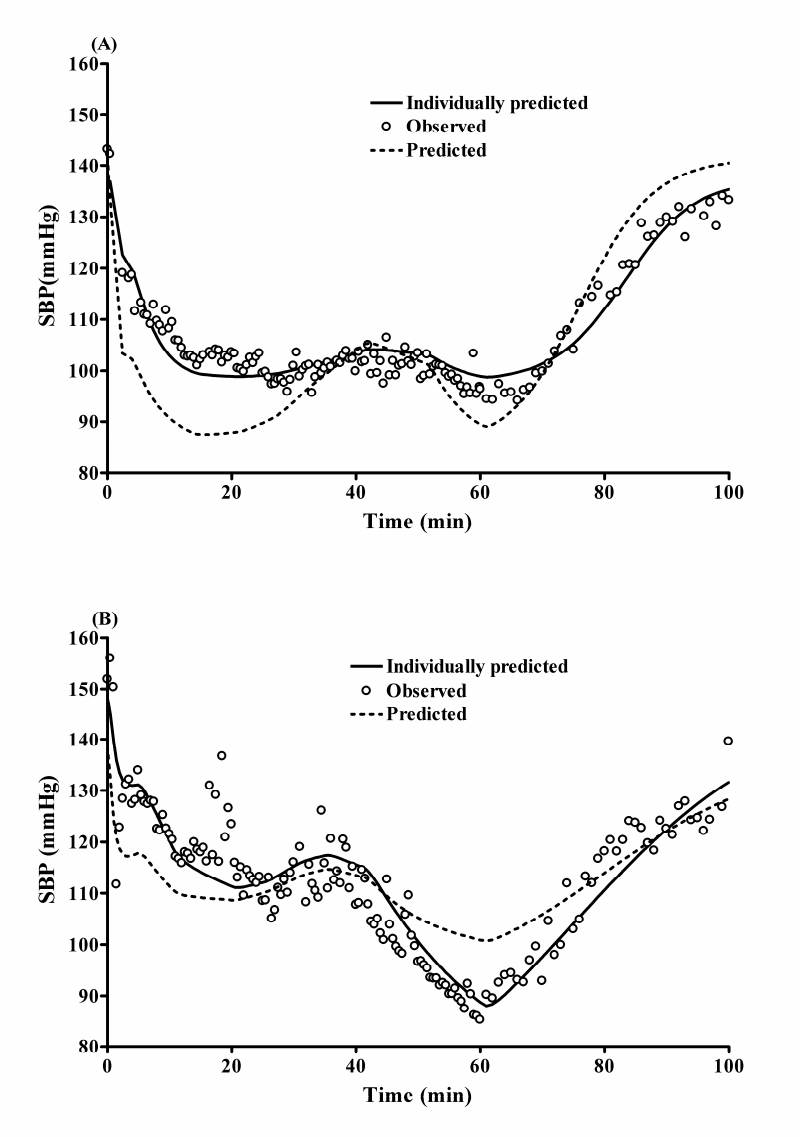


Figure 4. The change of observed, predicted and individually predicted systolic blood pressure (SBP) over time in volunteer ID 12.

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