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ORIGINAL COMMUNICATION

Individualization of the infusion rate of a soybean oil–based intravenous lipid emulsion for inpatients, based on baseline triglyceride concentrations: A population pharmacokinetic approach

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Abstract

Background: A rapid infusion rate for intravenous lipid emulsion (ILE) can cause adverse effects; therefore, safe and efficient infusion rates are desired. This study aimed to develop a triglyceride (TG) kinetic model after soybean oil–based ILE (SO-ILE) administration and individualize the infusion rate via a population pharmacokinetic approach.

Methods: Eighty-three inpatients were enrolled in this prospective observational study. A TG kinetic model was applied to the observations based on population pharmacokinetics using a nonlinear mixed-effect model. The patients' characteristics and laboratory parameters were evaluated to identify predictors of TG kinetics, and the maximum acceptable infusion rate was defined as that for which the maximum TG concentration did not exceed 400 mg/dl in 90% of patients.

Results: No adverse events associated with SO-ILE administration were observed. The developed TG kinetic model explained the observed TG concentrations and identified the baseline TG concentration and body weight as predictors of TG kinetics. The estimated maximum acceptable infusion rates greatly varied among individuals, ranging from <0.01 to 0.3 g/kg/h.

Conclusion: The present study suggested the necessity and demonstrated the feasibility of individualizing the infusion rates of SO-ILE, using a population pharmacokinetic approach.

KEYWORDS
infusion rate, intravenous lipid emulsion, population pharmacokinetics, triglyceride

CLINICAL RELEVANCY STATEMENT

An infusion rate of intravenous lipid emulsion (ILE) exceeding the lipid metabolism capacity can lead to adverse effects. A triglyceride (TG) kinetic model after soybean oil–based ILE administration was developed using a population pharmacokinetic approach and revealed the cause-effect relationship between the infusion rate and TG concentration in plasma and identified 2 influencing factors: baseline TG concentration and body weight. This methodology demonstrated the feasibility of individualizing the infusion rates of ILE.

INTRODUCTION

Intravenous lipid emulsion (ILE) is an important component of parenteral nutrition regimens as a source of nonprotein energy and essential fatty acids. Despite its clinical usefulness, using soybean oil–based ILE (SO-ILE) is often restricted by undesirable effects on inflammatory pathways, the immune system, and lipid metabolism,[1–3] which may be associated with fatty acid composition or ILE infusion rate.[4] Recently, alternative SO-ILE formulations comprising olive oil, fish oil, medium-chain triglycerides (TGs), or mixtures including soybean oil have been developed; they may provide benefits over SO-ILE regarding outcomes.[5–7] Conversely, the infusion rate must be restricted for all ILE formulations, as a rate exceeding the lipid metabolism capacity can cause hypertriglyceridemia, leading to fat overload syndrome, deep venous thrombosis, and acute respiratory distress syndrome.[8–10] Therefore, the lowest possible infusion rate of ILE is recommended for safe use.

A low infusion rate demands a long infusion time in return for safe ILE administration. Although safety is clinically the most important issue, the long infusion time of ILE may decrease patients' quality of life and increase nurses' workload. Additionally, ILE provides a favorable environment for microbial growth; the hanging time of ILE is considered a risk factor of infection.[11,12] Therefore, restricting the infusion rate for the safe use of ILE imposes other limitations in clinical settings; thus, an efficient administration of ILE is desirable.

Safe and efficient infusion rates of ILE for individuals have remained unclear. Reportedly, the adverse effects of long-chain TG–based ILE were only observed at infusion rates exceeding 0.11 g/kg/h,[13] whereas little information exists regarding the toxic concentrations of TGs. The adverse effects are not directly attributable to the infusion rates; instead, they are caused by increased TG concentrations in response to the infusion rate. Additionally, as the increases in TG concentrations following ILE administration should vary greatly between individuals, the same infusion rate cannot be recommended uniformly for all patients. Although the amount of ILE required is calculated for each patient based on the nutrition status, the infusion rate of ILE is not adjusted for patient characteristics, excluding critically ill patients. To our knowledge, there is no available information regarding how to adjust the infusion rate for each patient. To establish safe and efficient infusion rates of ILE for individuals, the cause-effect relationship between the infusion rate and TG concentration in plasma must be revealed and the factors influencing this relationship must be identified. We aimed to develop a TG kinetic model after SO-ILE administration and identify potential factors for individualizing the infusion rate for the safe and efficient use of ILE among inpatients.

METHODS

Patients

This prospective observational study was conducted at 2 institutions in Japan: Ageo Central General Hospital (Saitama) and Joetsu General Hospital (Niigata). Inpatients who initially received SO-ILE (Intralipos 20%) infusion were recruited between October 2016 and March 2018. Patient recruitment continued until the target number of patients (n = 45 per institution) was achieved or the trial period was terminated. Patients younger than 18 years, those with baseline TG concentrations exceeding 300 mg/dl, and those with incomplete data were excluded. Written informed consent was obtained from all patients in this study, and the study protocol was reviewed and approved by the ethics committee of both Ageo Central General Hospital (approval number: QIKR011-03) and Joetsu General Hospital (approval number: 2016–121).

Study design

The amount and infusion rate of SO-ILE were determined according to the individual clinician's judgment and experience. The basal energy expenditure (BEE) for individual patients was calculated using the Harris-Benedict equation, and then the total energy requirement (TER) was calculated by multiplying the BEE by a stress factor and an activity factor. The rates of lipid amount for the TER depended on the individual clinician; in the case of peripheral parenteral nutrition, for example, it was determined to be 44%–49% after determination of the TER by one clinician, and it was categorized as a regimen with an upper limit for fat of 2 g/d after determination of the protein dosage by another clinician. ILE infusion rates were manually set using a roller clamp; no further adjustments to the infusion rates were permitted during the SO-ILE infusion. The actual infusion rates were calculated from the fat dosages and observed infusion time. To minimize invasive procedures performed on the patients and to reveal TG kinetics during SO-ILE infusion, 2-point blood sampling was conducted for all patients, who were randomly allocated into 1 of the 3 groups based on their first blood sampling times. The first blood samplings were performed either within 1 hour, between 1 and 2 hours, or between 2 and 3 hours after the initiation of infusion in each group to obtain the population mean profile in the early phase. The second blood sampling was conducted at the end of the infusion in all groups to observe the maximum TG concentration (C_{max}) for individuals. The detailed process of the study design is described in the Supplementary Materials (Study Design). In addition to patient demographics, 20 laboratory parameters (see Table 1) were obtained via daily routine blood sampling

TABLE 1 Patients' demographics, SO-ILE dosing information, and laboratory parameters

	Data
Demographics	
Number of patients, n	83
Gender, male/female	44/39
Age, median [min, 25th, 75th, max], y	74 [20, 59, 82, 95]
Body weight, median [min, 25th, 75th, max], kg	55.8 [31.2, 46.2, 65, 86.1]
Primary diseases, n (%)	
Colon diverticulitis	10 (12.0)
Acute cholecystitis	9 (10.8)
Peptic ulcer	8 (9.6)
Ischemic colitis	7 (8.4)
Colorectal cancer	7 (8.4)
Intestinal obstruction	5 (6.0)
Colon diverticular bleeding	5 (6.0)
Acute enteritis	4 (4.8)
Gastric cancer	3 (3.6)
Ulcerative colitis	3 (3.6)
Pancreatic cancer	3 (3.6)
Cerebrovascular accident	3 (3.6)
Infectious enteritis	2 (2.4)
Constipation	2 (2.4)
Crohn's disease	2 (2.4)
Choledocholithiasis	2 (2.4)
Acute pancreatitis	2 (2.4)
Others	6 (7.2)
Comorbidity, n (%)	
Diabetes	9 (10.8)
Hyperlipidemia	8 (9.6)
SO-ILE dosing information, median [min, 25th, 75th, max]	
Dosage, g fat	50 [20, 40, 80, 120]
Infusion rate, g/kg/h	0.217 [0.053, 0.105, 0.278, 0.363]
Infusion time, h	5.2 [0.75, 3.0, 7.2, 19.8]
Laboratory parameters, median [min, 25th, 75th, max]	
TG, mg/dl	94 [30, 68, 119, 291]
T-chol, mg/dl	146 [74, 127, 193, 274]
HDL-chol, mg/dl	43 [18, 32, 60, 105]
LDL-chol, mg/dl	83 [17, 68, 114, 168]
Apolipoprotein CII, mg/dl	2.9 [1.2, 2.0, 4.0, 8.3]
Apolipoprotein CIII, mg/dl	7.0 [1.0, 4.6, 8.7, 18.2]
Apolipoprotein E, mg/dl	3.7 [1.5, 3.0, 4.3, 14.1]
Total protein, g/dl	6.6 [4.4, 6.1, 7.0, 8.5]
Serum Alb level, g/dl	3.52 [1.60, 2.90, 3.88, 4.76]
Blood glucose, mg/dl	114 [69, 99, 134, 245]
Insulin, μU/ml	7.2 [1.2, 3.8, 12.8, 135.4]
SUN, mg/dl	14.5 [6.3, 11.3, 21.5, 63.2]

(Continues)

TABLE 1 (Continues)

	Data
Scr, mg/dl	0.76 [0.31, 0.62, 0.89, 5.42]
AST, U/L	22 [8, 16, 33, 719]
ALT, U/L	19 [5, 12, 32, 425]
γ-GTP, U/L	24 [7, 15, 55, 967]
ALP, U/L	223 [98, 189, 279, 2643]
T-Bil, mg/dl	0.7 [0.2, 0.4, 1.2, 7.2]
D-Bil, mg/dl	0.3 [0.1, 0.2, 0.4, 6.0]
CRP, mg/dl	1.56 [0.02, 0.35, 5.85, 28.43]

Abbreviations: γ-GTP, γ-glutamyl transpeptidase; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; D-Bil, direct bilirubin; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; max, maximum; min, minimum; Scr, serum creatinine; SO-ILE, soybean oil–based intravenous lipid emulsion; SUN, serum urea nitrogen; T-Bil, total bilirubin; T-chol, total cholesterol; TG, triglyceride.

(approximately 6:00 AM) on the day of SO-ILE administration and the next day (ie, before and after administration). Laboratory parameters obtained during the SO-ILE infusion were excluded. If the elapsed time from the end of the SO-ILE administration could be precisely calculated, the TG concentrations obtained from the daily routine blood sampling on the next day were included in the TG kinetic analysis in addition to the 2-point blood sampling during SO-ILE infusion.

TG kinetic model

Three candidate models were tested, and the model that simplified our previous semiphysiological model in rats[14] was considered the best for the study purpose (see Model Selection in Supplementary Materials). In this model, the step in which artificial lipid emulsions in the SO-ILE formula acquire apolipoproteins immediately after administration was ignored, and they were not distinguished from endogenous lipoproteins in regard to lipid metabolism. The structure of the present TG kinetic model simply explains the mass balance of TGs in the systemic circulation. Because lipoproteins cannot pass through the blood vessels, TGs in lipoproteins can be distributed only into the plasma compartment, in which they are hydrolyzed by lipoprotein lipase and eliminated via first-order kinetics to be either catabolized or stored. Simultaneously, endogenous lipoproteins are reassembled in the liver and secreted into the plasma compartment with zero-order kinetics. Consequently, the mass balance of TGs in the systemic circulation can be described by the following differential equation:

$$\frac{dA}{dt} = EndVLDL - A \times Kel + InfRate, \quad (1)$$

where A is the amount of TGs (mg) in the plasma compartment; *EndVLDL* and *Kel* are the zero-order endogenous lipid production rate (mg/h) and first-order elimination rate constant (1/h), respectively; and *InfRate* is the infusion rate of SO-ILE (mg/h). The TG concentration in the systemic circulation, C, can be expressed using the plasma volume, V (dl), as follows: $C = A/V$.

Population pharmacokinetic and covariate analyses

To estimate parameters in the TG kinetic model, a population pharmacokinetic analysis was applied to the observations with a nonlinear mixed-effect model using the computer program NLME version 8.0 (Certara, MO, USA). The interindividual variability of a parameter was represented by the following exponential error model:

$$P_i = \theta_p \times \exp(\eta_P), \quad (2)$$

where P_i and θ_p are the individual values of the ith patient and the typical value of a parameter P in the population, respectively, and η_P is the random effect from a normal distribution at mean 0 and variance ω^2. The value of the plasma volume was fixed with the previously reported mean value of healthy individuals: body weight × 0.422 (dl).[15] The residual variability (including the intraindividual variability and measurement error) was characterized by the following proportional error model:

$$C_{Obs} = C \times (1 + \varepsilon), \quad (3)$$

where C_{Obs} and C represent the observed and predicted TG concentrations, respectively, and ε is the random error from a normal distribution at mean 0 and variance σ^2. The estimation of parameters was performed using the first-order conditional estimate-extended least-squares method.

Patient demographics and 20 laboratory parameters before the SO-ILE administration were evaluated as factors affecting TG kinetics—that is, covariates. Univariate analysis was conducted by individually introducing each candidate covariate into a null model in which no covariate was included (viz, base model), using the following power model with the covariate normalized to the population median:

$$P_i = \theta_p \times \left(\frac{Cov_i}{Cov_m}\right)^{\theta_{cov}}, \quad (4)$$

where θ_{cov} is the covariate effect, Cov_i is the covariate value for the ith patient, and Cov_m is the median value of the covariate in the study population. Binary covariates (0 or 1) were added using the following exponential model:

$$P_i = \theta_p \times \theta_{cov}^{Cov_i}, \quad (5)$$

The statistical significance of candidate covariates was evaluated using the objective function value (OFV, equal to −2 × log-likelihood value), which is an index of model fitness. If the addition of a candidate covariate reduced the OFV value by >6.63, it could be considered that the candidate covariate significantly improves model fitness ($P < .01$) based on the χ^2 test. The covariate selection was conducted via a stepwise forward-inclusion/backward-elimination approach. During forward selection, the covariate was added to the base model with the rank order of reduction of the OFV value in univariate analysis and was included if a significant reduction (>6.63) in the OFV value ($P < .01$) from the nest model was obtained. Subsequently, a covariate was eliminated independently from the full model and was retained if a significant increase (>10.83) in the OFV value ($P < .001$) was observed. Consequently, the final model was decided on the basis of statistical significance, physiological plausibility, and clinical usefulness.

Final model validation and nomogram for the maximum acceptable infusion rate

The fitness and model performance of the final model were visually evaluated by goodness-of-fit plots and the prediction-corrected visual predictive check (pcVPC),[16] respectively (Supplementary Materials). The accuracy and robustness of the estimates of the final model were evaluated using a nonparametric bootstrap method. The bootstrap data sets (n = 1000) were generated by resampling the patients with replacement from the original data set. The estimates from the original data set were compared with the median and 95th percentile confidence interval (95th CI) of estimates obtained from the bootstrap data sets.

In the development of the nomogram, the maximum acceptable infusion rate was defined as the infusion rate at which the C_{max} for the 90th percentile of patients did not exceed 400 mg/dl. At C_{max} during the infusion, the left side of Equation (1) is 0. Therefore, the population mean of C_{max} can be expressed as

$$C_{max} = \frac{EndVLDL + InfRate}{V \times Kel}, \quad (6)$$

Subsequently, to evaluate the propagation of the interindividual and the residual variabilities in the final model to the population mean of C_{max}, a 10,000-person Monte Carlo simulation was conducted with the estimates of the final model, and then, the ratio of the 90th percentile of C_{max} to the population mean was obtained. This procedure was repeated 9 times under different conditions for the infusion rate and selected covariates. In this manner, the mean value of the propagation was obtained. The target population mean of C_{max} for the propagation of variabilities was adjusted. The prediction formula of the maximum acceptable infusion rate was obtained by substituting the model structure and population mean values of parameters into Equation (6). Thus, the nomogram was developed to easily and roughly predict the individual maximum acceptable infusion rate of SO-ILE.

TABLE 2 Univariate analysis of candidate covariates

Candidate covariate[a]	Linear correlation with η	ΔOFV[b]
Baseline TG on Kel	−0.557	−29.1
Apolipoprotein CIII on Kel	−0.508	−24.5
Apolipoprotein CII on Kel	−0.500	−22.8
Body weight on Kel	−0.373	−15.7
Serum Alb level on Kel	−0.392	−12.8
Body weight on EndVLDL	0.392	−12.6

Abbreviations: ΔOFV, change in the objective function value; Alb, albumin; EndVLDL, zero-order endogenous lipid production rate; Kel, first-order elimination rate constant; TG, triglyceride.
[a]Candidate covariate was introduced into the base model using Equation (4) or (5).
[b]A decrease of >6.63 indicated statistical significance ($P < .01$).

RESULTS

Overall, 84 inpatients (39 and 45 from the 2 institutions) were registered; 1 patient was excluded owing to incomplete data. All patients received ILE infusion via peripheral (n = 75) or central venous (n = 8) catheters during parenteral nutrition. Patients' demographics, SO-ILE dosing information, and laboratory parameters in this study are summarized in Table 1. The most common primary disease was inflammatory disease, and most participants had acute illness characterized by low serum albumin (Alb) and high C-reactive protein (CRP) levels. In total, 238 TG concentrations were measured in 83 patients, of which 72 concentrations were obtained from the daily routine blood sampling conducted on the next day. The obtained TG concentration profiles are shown in Figure 1 (an enlarged view of the early phase after the infusion is presented in Figure S2). Although there was large interpatient variability in TG concentrations during the SO-ILE infusion, most concentrations returned to the baseline levels on the next day after the infusion. There were no significant differences in laboratory parameters before and after SO-ILE administration (data not shown), and no adverse events associated with its administration were reported. The result of univariate analysis is listed in Table 2 in order of decreasing OFV. In a stepwise covariate model, the reduction of OFV observed by including apolipoprotein CIII, CII, or serum Alb levels in Kel after the inclusion of the baseline TG concentration (−7.6, −4.4, and −6.3, respectively) was smaller than that observed in univariate analysis (Table 3, models 2, 3, and 5). In addition, after the inclusion of baseline TG levels and body weight in Kel (model 4), the reduction of OFV by including body weight in EndVLDL was not statistically significant (model 6). Therefore, model 4 was selected as a full model.

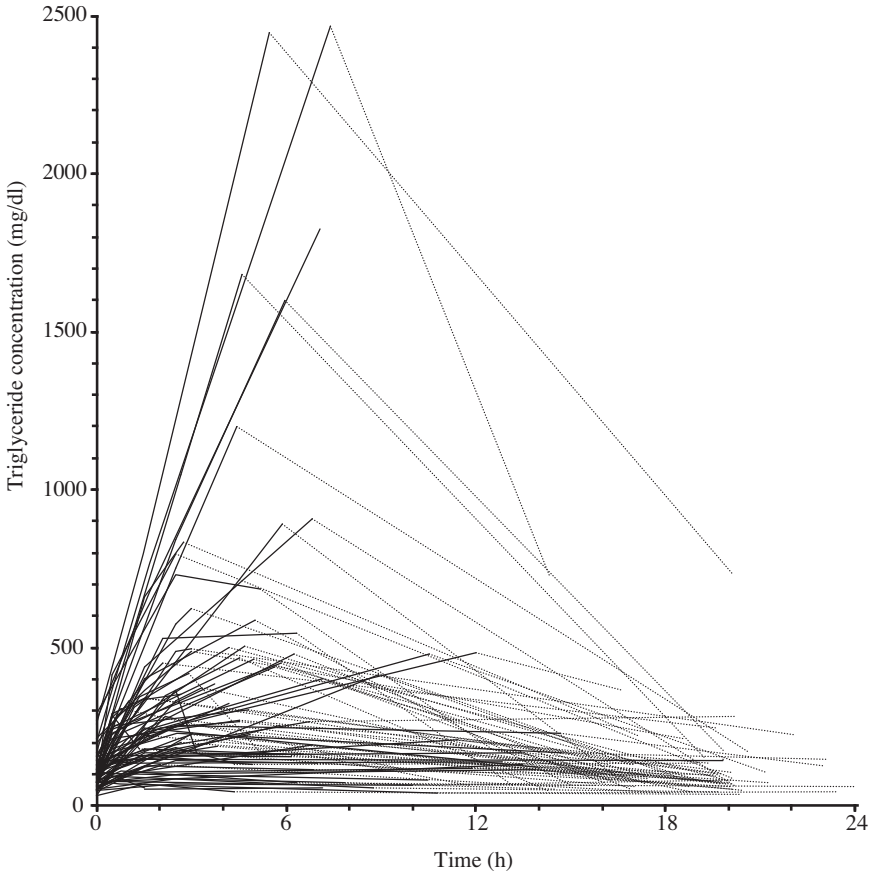

FIGURE 1 Observed triglyceride concentrations after soybean oil–based intravenous lipid emulsion administration. Solid lines indicate the profiles during infusion, and dashed lines connect the concentrations at the end of the infusion to the following day

TABLE 3 Stepwise covariate modeling

Model number	Model description	ΔOFV
Forward inclusion		
0 (Base model)	–	–
1	Baseline TG on Kel	−29.1
2	Baseline TG and apolipoprotein CIII on Kel	−7.6
3	Baseline TG and apolipoprotein CII on Kel	−4.4
4 (Full model)	Baseline TG and body weight on Kel	−26.3
5	Baseline TG and serum Alb level on Kel	−6.3
6	Baseline TG and body weight on Kel and body weight on EndVLDL	−5.8
Backward elimination		
7	Full model—baseline TG on Kel	40.2
8	Full model—body weight on Kel	27.0
9 (Final model)	Full model—$\eta_{EndVLDL}$	0.0

Abbreviations: ΔOFV, change in the objective function value; $\eta_{EndVLDL}$, interindividual variability of EndVLDL; Alb, albumin; EndVLDL, zero-order endogenous lipid production rate; Kel, first-order elimination rate constant; TG, triglyceride.

In a backward-elimination approach, the eliminations of baseline TG levels and body weight from the full model significantly increased OFV, whereas the elimination of the interindividual variability of EndVLDL, $\eta_{EndVLDL}$, had no effect (model 9). This model was selected as the final model. The goodness-of-fit and pcVPC plots are shown in Figures S4 and S5, confirming accurate and unbiased predictions of the final model. The estimates of the final model and the result of the bootstrap validation are summarized in Table 4. The estimated values obtained from original data set were similar to the median values of bootstrap replications (n = 1000), indicating the accuracy and robustness of the estimates of the final model. With a 10,000-person Monte Carlo simulation using the final model under different conditions for

TABLE 4 Final estimates of TG kinetic model and bootstrap validation

		Original data set		Bootstrap replication, n = 1000		
	Unit	Estimate	RSE, %	Median	95th CI	Bias,[a] %
Final model structure						
V (dl) = 0.422 × body weight						
EndVLDL (mg/h) = θ1						
Kel (1/h) = θ2 × (TG_{base}/TG_{base}, median)$^{\theta 3}$ × (body weight/body weight, median)$^{\theta 4}$						
Population mean, θ						
θ1	mg/h	5709	11.4	5707	4568–7103	0.03
θ2	1/h	2.51	10.3	2.50	2.06–3.10	0.19
θ3	-	−0.833	14.9	−0.832	−1.088 to −0.591	0.09
θ4	-	−1.27	20.0	−1.27	−1.77 to −0.72	0.30
Interindividual variability[b], ω						
ω_{Kel}	%	43.3	8.0	42.1	34.4–49.6	2.82
Residual variability[c], δ						
δ	%	31.8	6.4	31.6	27.6–35.6	0.78

Note: The median values of TG_{base} and body weight were 94 mg/dl and 55.8 kg, respectively.
Abbreviations: 95th CI, 95th percentile confidence interval; EndVLDL, zero-order endogenous lipid production rate; Kel, first-order elimination rate constant; RSE, relative standard error; TG_{base}, baseline triglyceride concentration.
[a]Bias (%) = (estimated value from original data set − median estimated value from bootstrap replications)/estimated value from original data set × 100.
[b,c]Interindividual variability and residual variability was introduced using Equation (2) and (3), respectively.

the infusion rate and the selected covariates, the mean ratio of the 90th percentile to the population mean of C_{max} was 1.894 ± 0.014. Considering this propagation of variabilities in the final model, the target population mean of C_{max} was adjusted to 211 mg/dl (= 400/1.894). Thereafter, the obtained prediction formula for the maximum acceptable infusion rate was as follows:

$$\begin{aligned} &\textit{Maximum acceptable infusion rate } (g/h) = [211 \times \theta 2 \\ &\quad \times (TG_{base}/TG_{base,\,median})^{\theta 3} \times (bodyweight/bodyweight_{median})^{\theta 4} \\ &\quad \times 0.422 \times body\ weight - \theta 1] \div 1000 \end{aligned} \tag{7}$$

where the population mean (from θ1 to θ4) and the median values of TG_{base} and body weight were shown in Table 4. Figure 2 represents a nomogram developed from Equation (7), and Figure S5 shows an overlay plot of the individual patients in this study population on the nomogram. Figure 3 depicts a histogram of the estimated maximum acceptable infusion rates for individual patients (n = 83) in this study using Equation (7).

DISCUSSION

Considering the primary diseases and the low serum Alb and high CRP levels observed in this study, poor nutrition status caused by primary diseases and inflammation appeared to be one of the primary characteristics of this study population. The actual ILE infusion rates showed a wide range (some rates exceeded routine practice; Table 1). Because of the study's purpose to reveal the cause-effect relationship between the ILE infusion rate and TG concentration, the actual infusion rates, not the nominal infusion rates (ie, the clinician's order), were calculated by the dosage and infusion time under the limitation that no adjustment was permitted after the infusion started manually. The observed wide range in the actual ILE infusion rate must be due to strict adherence to the study protocol. On the next day after SO-ILE administration, most TG concentrations returned to the baseline levels. In addition, the lack of changes in laboratory parameters after the infusion and the absence of adverse events suggested that SO-ILE was tolerated well in this study.

In this study, we adapted the simplified TG kinetic model assuming first-order elimination, although we strongly suspected lipid metabolism at some observed TG concentrations (>1000 mg/dl) to be saturated. We previously reported that the semiphysiological kinetic model integrated a saturable manner to reveal TG kinetics, even with excessive infusion rates, such as lipid rescue therapy. In this study, to individualize the ILE infusion rate for safe and efficient use of ILE, the target population mean of C_{max} was set to 211 mg/dl, at which the TG concentration is unlikely to saturate lipid metabolism. Therefore, the simplification of TG kinetics assuming first-order elimination was analytically possible and clinically suitable for the study purpose. The effect of high TG concentrations on the results is discussed in Supplementary Materials (see the Sensitivity Analysis Excluding Observations of High TG Concentration section). In addition, the plasma volume was fixed with the previously reported mean value of healthy individuals; there was no evidence that the body composition of our patients was comparable to that of healthy individuals. However, if the plasma volume was fixed just close to true 1, the value itself (0.422 dl/kg) had no clinical significance to achieve the study purpose. The effect of

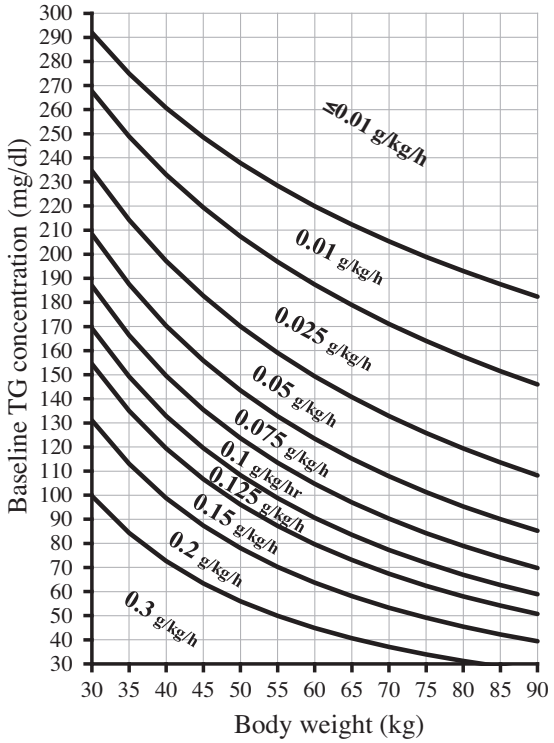

FIGURE 2 Nomogram for predicting the individual maximum acceptable infusion rate of soybean oil–based intravenous lipid emulsion based on the baseline triglyceride (TG) concentration and body weight. The maximum acceptable infusion rate for a patient is indicated by the value (g/kg/h) in the area including the point of intersection of the baseline TG concentration and body weight. For instance, in the case of a typical patient (baseline TG, 94 mg/dl; body weight, 55.8 kg), the point of intersection of the baseline TG concentration and body weight is located in the area of 0.125 g/kg/h, which is the maximum acceptable infusion rate for this patient

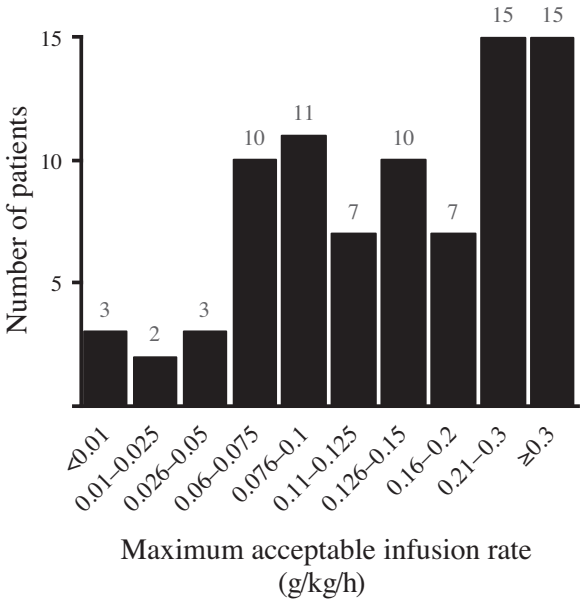

FIGURE 3 Histogram of the estimated maximum acceptable infusion rates for individual patients (n = 83) in the present study using Equation (7)

plasma volumes on the results is discussed in Supplementary Materials (see the Sensitivity Analysis Varying the Fixed Values of Plasma Volume section). As it is known that apolipoprotein CIII inhibits the activity of lipoprotein lipase,[17] the finding of a negative correlation between Kel and apolipoprotein CIII was reasonable; however, a similar correlation was also observed with apolipoprotein CII, which is known to stimulate the activity of lipoprotein lipase.[18] Although Erkelens et al reported that the amount of apolipoprotein CII bound did not control the rate of infused TG removal from plasma,[19] the negative correlation found in this study could not be explained by this previous report. Considering the observed collinearity between baseline TG and apolipoprotein CII and CIII (data not shown) in addition to the negative correlation between serum Alb level and Kel, the amounts of these apolipoproteins might not functionally relate to the value of Kel after SO-ILE administration, but it may simply reflect the hypermetabolism in patients induced by the primary disease and/or invasion and inflammation before administration. Therefore, the baseline TG concentration was selected as the most effective predictor for Kel among these candidate covariates in this study. This finding was entirely in line with early reports.[19–21] Meanwhile, Saiki et al reported a negative correlation between body weight and preheparin lipoprotein lipase mass,[22] and Mittendorfer et al reported a positive correlation of fat-free mass with the secretion rate of very low-density lipoprotein.[23] Our findings regarding body weight were in accordance with these previous reports; however, after the inclusion of body weight in Kel, the subsequent inclusion of body weight in EndVLDL failed to significantly decrease OFV. Because EndVLDL should have relatively weaker effects on the TG concentration in plasma during the infusion of ILE, it appeared difficult to accurately estimate the interindividual variability in EndVLDL under the present study design, in which most blood samplings for TG were performed during the infusion of ILE. Therefore, because of this limitation in the present study design, it appeared mathematically plausible that the effect of body weight on EndVLDL was explained by that on Kel.

The final model was validated by the results of goodness-of-fit plots, pcVPC, and bootstrap validation. To predict the maximum acceptable infusion rate, it is first essential to determine whether high TG concentrations are acceptable. As it was reported that all of the adverse effects associated with long-chain TGs occurred with infusion rates exceeding 0.11 g/kg/h,[13] most international guidelines are roughly compliant with this infusion rate.[24,25] However, there is no international criterion regarding acceptable TG concentrations during the infusion of ILE. The guidelines of the Japanese Society for Parenteral and Enteral Nutrition state that serum TG levels ranging from 300 to 400 mg/dl are acceptable during the infusion of ILE,[26] and the guidelines of the German Association for Nutritional Medicine for parenteral nutrition also state that serum TG levels of approximately 400 mg/dl can be reached postprandially and are considered acceptable during the infusion of ILE.[27] According to these guidelines, the TG concentration of 400 mg/dl was regarded as the maximum acceptable TG concentration during the SO-ILE infusion in this study; however, this value is not based on solid evidence and further studies are necessary to evaluate it. Second, the interindividual and residual

variabilities should be considered when determining acceptable TG concentrations. These variabilities need to be obtained from patients as opposed to healthy volunteers. Accordingly, the maximum acceptable infusion rate was set to ensure that C_{max} did not exceed 400 mg/dl for 90% of patients. Under this condition, the population mean of C_{max} (211 mg/dl) was lower than the theoretical increase in the TG concentration immediately after the intravenous fat tolerance test (237 mg/dl), which was calculated by dividing the dosage (0.1 g/kg) by the plasma volume (0.422 dl/kg), and was comparable to the preestablished abnormal TG response after the oral fat tolerance test (>220 mg/dl).[28] Moreover, the maximum acceptable infusion rate for a typical patient in this study was consistent with the current recommendations of guidelines, suggesting that the prediction of the maximum acceptable infusion rate in this study was appropriate. It should be noted here that 30 patients could be adapted to infusion rates exceeding 0.2 g/kg/h, and conversely, 8 patients required infusion rates of <0.05 g/kg/h (Figure 3), implying the necessity of individualizing the ILE infusion rate. The present study demonstrated the feasibility of individualizing SO-ILE infusion rates using a population pharmacokinetic approach. The nomogram presented herein is not intended for other institutions but methodologically demonstrates the conversion of the results from this approach into "clinical site–friendly" tools. In addition, the nomogram presented does not necessarily facilitate more rapid infusions and the estimated maximum acceptable infusion rate is never recommended to be used routinely.

Two limitations of this study warrant mention. The first involves the study population, as all participants in this study were Japanese adult inpatients. In addition, hypermetabolism was suspected in most patients, which might enable this population to be analyzed by first-order kinetics. Therefore, the present results cannot be easily extrapolated to other populations such as pediatric patients and patients receiving home parenteral nutrition. The other limitation is that inherent to kinetic analysis. Although a TG clamp technique experimentally proved the saturation of apolipoprotein acquisition at a rapid ILE infusion rate,[29] no obvious saturation was detected in the present study. Three reasons for this finding were considered: (1) the number of blood samples was insufficient; (2) at a rapid infusion rate, the infusion of SO-ILE could be completed before obvious saturation was detected; and (3) large interindividual variability could overwhelm the nonlinear kinetics of TG at a rapid infusion rate. Therefore, the present approach and results should be further validated in other populations and be modified, as appropriate. In addition, not only ILE infusion rates but also plasma TG concentrations responsible for adverse effects should be focused on to reveal the cause-effect relationship between TG concentrations and adverse effects as the next step toward optimizing safe and efficient ILE infusion rates.

CONCLUSION

The developed TG kinetic model explained well the cause-effect relationship between the infusion rate and plasma TG concentration and identified baseline TG concentrations and body weight as predictors of plasma TG concentrations after SO-ILE infusion. The present study suggested the necessity and demonstrated the feasibility of individualizing SO-ILE infusion rates using a population pharmacokinetic approach.

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CONFLICT OF INTEREST

None declared.

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AUTHOR CONTRIBUTIONS

Keizo Fukushima, Kenji Omura, Satoshi Goshi, Takae Tsujimoto, Keiji Iriyama, and Nobuyuki Sugioka contributed to the conception and design of the research; Kenji Omura, Satoshi Goshi, and Motomu Tanaka contributed to the acquisition of the data; Keizo Fukushima, Akira Okada, and Nobuyuki Sugioka contributed to the analysis of the data; Kenji Omura, Satoshi Goshi, and Keiji Iriyama contributed to the interpretation of the data; and Keizo Fukushima and Nobuyuki Sugioka drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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SUPPORTING INFORMATION

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