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Research Article

Pharmacokinetic-Pharmacodynamic Analyses of the Antidiabetic Drug, Nateglinide, in Goto-Kakizaki Rats Based on Pharmacological Mechanism

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ABSTRACT

Background: Quantitative understanding of the Pharmacokinetics (PK) and pharmacological effects/side effects of antidiabetic drugs is important for preventing serious complications. We investigated the PK of nateglinide, a rapid and short-lived insulin release model drug, in type 2 diabetes model rats, analysing the time profiles of plasma insulin and glucose levels. Using PK and Pharmacodynamics (PD) analysis, we quantitatively investigated relationship between nateglinide PK and its PD.

Methods: Nateglinide was administered to rats, and blood samples were subsequently collected for PK, insulin, and glucose analyses. PK and PK-PD model analyses of nateglinide were then performed.

Results: The 3-compartment model exhibited slightly better at low plasma concentrations compared to the 2-compartment model. However, low plasma nateglinide concentrations minimally affected plasma insulin and glucose levels. The change in insulin was almost proportional to the plasma nateglinide concentration, and no hysteresis was observed. In contrast, delayed hysteresis was observed between plasma insulin and glucose concentrations, which may be explained by the insulin resistance of the type 2 diabetes model rat.

Conclusion: The PK/PD model for nateglinide was successfully established based on its pharmacological mechanism. This model will enable the estimation of variations in the effects induced by various PK changes.

Keywords: Pharmacokinetic-pharmacodynamic modelling; Nateglinide; Insulin; Glucose; Goto-Kakizaki rats

INTRODUCTION

The efficacy of drug therapy is clinically assessed by measuring plasma concentration, which serves as a proxy for pharmacological effects and potential side effects. Understanding the correlation between drug plasma concentration and its effects is crucial for evaluating therapeutic effects over time in clinical practice. A Pharmacokinetic (PK)-Pharmacodynamic (PD) (PK-PD) model offers a temporal quantitative analysis of the relationship with drug plasma concentration, and of the effect and/or side effects of drug administration, at a given dosage. PK-PD analyses have been performed for several drugs, providing substantial information for managing drug therapy and determining therapeutic doses, dosing regimens, and optimizing individualized treatment plans [1-5].

Diabetes, a prevalent metabolic disorder, is characterized by an increasing number of patients with symptoms of hyperglycemia. Hyperglycemia results from issues in insulin secretion, insulin action, or both. Diabetes is classified into two types: Type 1 and type 2, insufficient insulin secretion causes type 1 diabetes, whereas decreased insulin sensitivity causes type 2 diabetes. Chronic hyperglycemia due to therapeutic failure increases the risk of neuropathy, retinopathy, and considerable neurological dysfunction in patients with diabetes [6-8]. Therefore, quantitatively understanding the PK, pharmacological effects, and side effects of drugs is necessary to maintain an appropriate dosage in diabetes therapy.

We previously used PK-PD models to investigate the relationship between PK and the hypoglycemic effects of glimepiride, a drug used to treat type 2 diabetes mellitus, using normal Wistar rats, streptozotocin-induced type 1 Wistar rats, and Goto-Kakizaki (GK) rats as type 2 diabetes models [9]. The characteristics of the normal and disease models were subsequently compared. Glimepiride is widely used as a therapeutic drug for type 2 diabetes in clinical practice and has also been reported to be effective for type 1 diabetes (data on file, (2017) Interview Form, Amaryl, Sanofi K. K.). Furthermore, it induces endogenous insulin secretion and decreases blood glucose levels [10]. The PD model in this study adopted a simple sigmoid E_{max} model that was able to relate glimepiride and hypoglycemic effects. However, since this PD model is not based on the pharmacological action, its scope of

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application is limited, and it is difficult to apply it to change in pathological conditions.

Nateglinide is an amino acid derivative of D-phenylalanine that stimulates insulin secretion by binding to ATP potassium channels in pancreatic β-cells. Consequently, β-cell calcium influx increases, leading to rapid and short-lived insulin release and a decrease in the plasma glucose concentration [11]. This increase in insulin secretion quickly returns to baseline levels. Nateglinide reduces fasting and mealtime blood glucose levels in animals, healthy volunteers, and patients with type 2 (non-insulin-dependent) diabetes mellitus [11-16]. It subsequently generates prompt prandial insulin responses with insulin levels returning to baseline levels between meals.

Herein, nateglinide PK and its effects were investigated in a type 2 diabetes GK rat model to explain the relationship between nateglinide PK and PD. We attempted to further evolve a previously published PK-PD model of glimepiride, aiming to create an improved model that considers the actual pharmacological mechanism. Specifically, we incorporated insulin dynamics into the model. Nateglinide increased plasma insulin, which lowered plasma glucose in sequence. Additionally, time profiles of plasma glucose in relation to plasma nateglinide and insulin concentrations were investigated. The PK-PD model was used to explain the time-dependent pharmacodynamic effects produced by the plasma drug concentration profiles. Therefore, these models describe the time-dependent effects of plasma drug concentration profiles.

MATERIALS AND METHODS

Materials

Nategrinide and acetonitrile, of High-Performance Liquid Chromatography (HPLC) grade, were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). Polyethylene Glycol 400 (PEG) was purchased from Nacalai Tesque Inc. (Kyoto, Japan). All other reagents were of analytical grade and were commercially obtained. Standard nategrinide stock solutions were prepared by dissolving nategrinide in methanol at a 1.0 mg/ml concentration. This solution was subsequently used to prepare a standard calibration curve. A small amount of this solution was added to drug-free rat plasma.

Animal experiments

Male GK rats (Shimizu Laboratory Co., Ltd., Kyoto, Japan) of 9-11 weeks old (290-305 g) were used as a polygenic model of spontaneous type 2 diabetes mellitus. Animal experiments were performed in accordance with the Guidelines for Animal Experiments of Doshisha Women's College of Liberal Arts. This guideline follows the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions (Ministry of Education, Culture, Sports, Science and Technology, Notice No. 71), Guidelines for Proper Conduct of Animal Experiments (Science Council of Japan). Rats were housed in pairs under controlled environmental conditions and fed commercial feed pellets with water provided ad libitum. Five to six rats were used in this study.

Under anesthesia by Intraperitoneal (IP) somnopentyl injection (Kyoritsu Seiyaku Corporation, Tokyo, Japan, 32.4 mg/kg rat body weight), Intravenous (IV) infusion solutions of nateglinide dissolved in 0.5 ml PEG were administered at a dose of 10.0 mg/kg rat body weight. Furthermore, although nateglinide is an orally administered drug, we used an intravenous administration method that eliminated the absorption process, as this study aimed to examine the time course of plasma concentration and its effects. Additionally, we used Intravenous (IV) infusion as the administration route to investigate the time course of the effect when the plasma concentration first increased and subsequently decreased. The test solutions were infused into the right femoral vein for 30 min at an infusion rate of 0.5 ml/30 min using a variable-speed compact infusion pump (KDS1000 syringe pump; LMS Co., Ltd, Tokyo, Japan). Blood samples were directly collected from the right jugular vein using a heparinized syringe 5-360 min after initiating the infusion. All blood samples were centrifuged to obtain plasma fractions. Plasma samples were immediately stored in a freezer at -30°C until PK and insulin analyses, or stored in the refrigerator for glucose analysis.

Quantitative analysis of nateglinide

Nateglinide was extracted from rat plasma for analysis. To a 15 ml glass extraction tube, was shaken for 20 min and centrifuged to separate the organic layer from the aqueous solution. Organic extracts were separated by freezing the aqueous layer and decanting the organic liquid into clean glass tubes. The organic liquids were evaporated using an SPD1010 SpeedVac concentrator system (Thermo Electron Corporation, Yokohama, Japan). The resulting residue was re-dissolved by adding 50 µl of the HPLC mobile. phase (acetonitrile: 0.1% formic acid =90:10), of which a 30-µl aliquot was injected into the liquid chromatography-tandem mass spectrometry system (LC-MS/MS) described below. Calibration curve samples were prepared by adding known amounts of nateglinide (0.2-1200 ng) to drug-free rat plasma.

Plasma nateglinide concentrations were determined using an LCMS 8050 LC-MS/MS system (Shimadzu Co., Kyoto, Japan) equipped with a Prominence HPLC system (Shimadzu). The HPLC system consisted of two LC-20AD pumps and a SIL-20AC automatic sample injector. The pump flow rate was 0.2 ml/min. The analytical column was a Cosmosil $5C_{18}$-MS-II (50 × 2.0 mm ID; Nacalai Tesque Inc.) and was maintained at 40°C using a CTO-20A column oven (Shimadzu). The data were loaded onto the Lab Solutions ver. 5.91 analytical software (Shimadzu) by connecting to a CBM-20A (Shimadzu) communication bus module. Detection was performed in the multiple reaction monitoring (MRM) mode of the parent and the selected product ions acted in the positive mode. Nateglinide was monitored using m/z 318.1 → 69.0 mass transitions by Electrospray Ionization (ESI). The linear range of the calibration curve was between 10 and 20,000 ng/ml.

Quantification of plasma insulin and glucose

Plasma insulin concentrations were measured using the enzyme-linked immunosorbent assay sandwich method with an insulin measurement kit (Morinaga Institute of Biological Science, Inc., Kanagawa, Japan), following the manufacturer's instructions. Briefly, sample plasma (5 µl) was added to a well plate and kept at 4°C for 2 h. Subsequently, 100 µl of anti-insulin antibody-reacting solution was added to the plate and maintained at 25°C for 30 min. Next, 100 µl of the substrate solution for the enzyme assay was added, and the wells were incubated at room temperature in dark for 40 min. The reaction was stopped by adding 100 µl of stop solution and the absorbance was measured at 450 nm within 30 min.

Plasma glucose concentrations were measured by the glucose oxidase method using the glucose CII test (Wako Pure Chemical

Industries, Ltd.), following the manufacturer's instructions. Briefly, 10 µl of the plasma sample was added to a clean glass tube, and a glucose-reacting solution (1.5 ml) was added to the tube. The tube was subsequently vortexed for 1 min and incubated at 37°C for 5 min, and the absorbance was measured at 490 nm within 30 min.

PK analysis

Non-compartmental PK analysis was performed using Phoenix 64 WinNonlin version 8.3.3.33 (Pharsight Corporation, Mountain View, CA, USA) to obtain the basic PK parameters. The terminal elimination rate constant, ke, of the nateglinide concentration-time profile was determined using linear regression of at least three data points from the terminal period of the plasma concentration-time plot. The Area Under the Curve (AUC) plasma concentration-time after Intravenous (IV) infusion was calculated using the linear trapezoidal rule up to the last measured plasma concentration, clast, and extrapolated to infinity by adding a correction term. The terminal elimination half-life, $t_{1/2}$, was determined by dividing ln2 by ke. The Area Under the Moment Curve first (AUMC) after nateglinide administration was calculated using the linear trapezoidal rule up to Clast and a correction term was added after the last measurement point to infinity. Total plasma clearance (CL_{tot}) and Mean Residence Time (MRT) were determined by dividing the administered Dose (D) by the AUC and AUMC/AUC-$T_{inf}/2$, respectively, where T_{inf} is the infusion duration (30 min). The distribution volume at steady state, V_{dss}, was calculated using CL_{tot}/k_e.

General 2 and 3 compartmental PK models were applied to the data using Phoenix 64 WinNonlin to fit the data to the models (Figure 1). These models have the following assumptions: Rate constants of the PK process (k_{12}, k_{21}, k_{13}, k_{31}, and ke) followed first-order kinetics, nateglinide infusion rate (K_0) followed zero-order kinetics, V_1 is the volume distribution in the central compartment, and indices 1-3 represent the number of PK compartments.

PK-PD analysis

The hypoglycemic effect of nateglinide was estimated based on its pharmacological mechanism (Figure 1). PK-PD analyses of nateglinide-induced plasma insulin and insulin-induced glucose changes were performed using ordinary indirect response models. When the obtained data were fitted to both PD models, the control effects (an effect in which only solvent was administered instead of the drug and the same experiments were performed) on the insulin and glucose profiles were subtracted from the raw plasma insulin and glucose levels after nateglinide administration. The PD parameters were predicted in sequence by fitting the data to PK-PD models using WinNonlin by incorporating the PK parameters determined from the plasma values. In the model, K_{in} and k_{out} are the zero- and first-order rate constants of the formation and elimination of insulin/glucose, respectively. The maximum drug effect (E_{max} or I_{max}), drug concentration at the half-maximum effect (EC_{50} or IC_{50}), and Hill constant (γ) are the constants for ordinary sigmoid E_{max} models. The PK-PD parameters and subscripts I and G indicate the values for insulin and glucose, respectively. The average of the measured baseline values of insulin or glucose was used as the initial insulin and glucose values. These values were used to calculate K_{in}/k_{out} for model fitting. Initial values of insulin and glucose were 1.91 ng/ml and 351 mg/dl, respectively.

Nateglinide to insulin

$$dC_{Inslin}/dt = K_{inI}\left(1+\left(E_{\max I}\times C_{nateglinide}{}^{\gamma I}\right)/\left(EC_{50I}{}^{\gamma I}+C_{nateglinide}{}^{\gamma I}\right)\right)-K_{outI}\times C_{Inslin} \quad (1)$$

Insulin to glucose

$$dC_{Glucose}/dt = K_{inG}\left(1-\left(I_{\max G}\times E_{Ins}{}^{\gamma G}\right)/\left(E_{Ins}{}^{\gamma G}+IC_{50G}{}^{\gamma G}\right)\right)-K_{outG}\times C_{Glucose} \quad (2)$$

RESULTS

PK study of nateglinide

Figure 2 illustrates the plasma concentration-time profile and fitting curves after 30 min Intravenous (IV) nateglinide infusion in GK rats. The inset shows the profile in the low-concentration range. The plasma concentration of the drug increased during infusion and subsequently decreased rapidly before slowing after infusion was terminated.

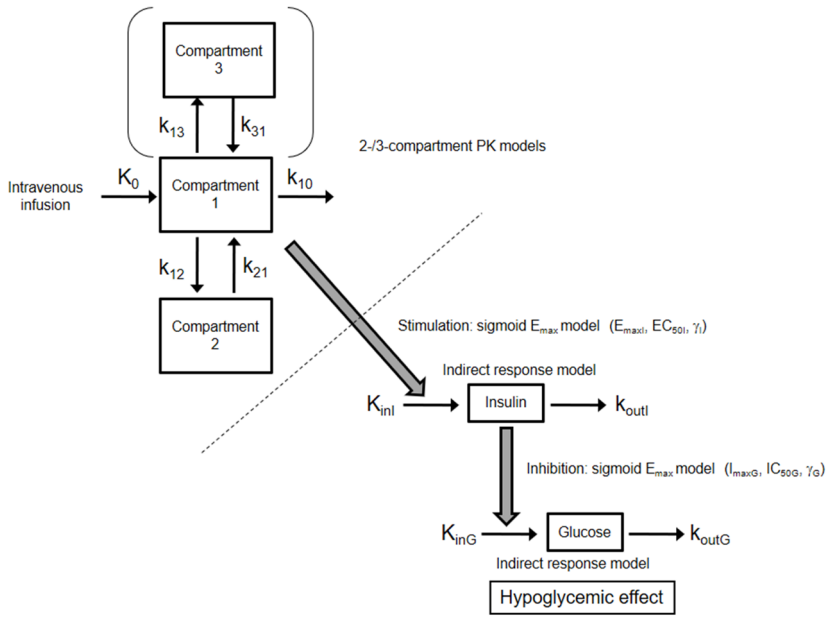

Figure 1: Schematic representation of the pharmacokinetic-pharmacodynamic model of insulin and glucose changes produced by nateglinide.

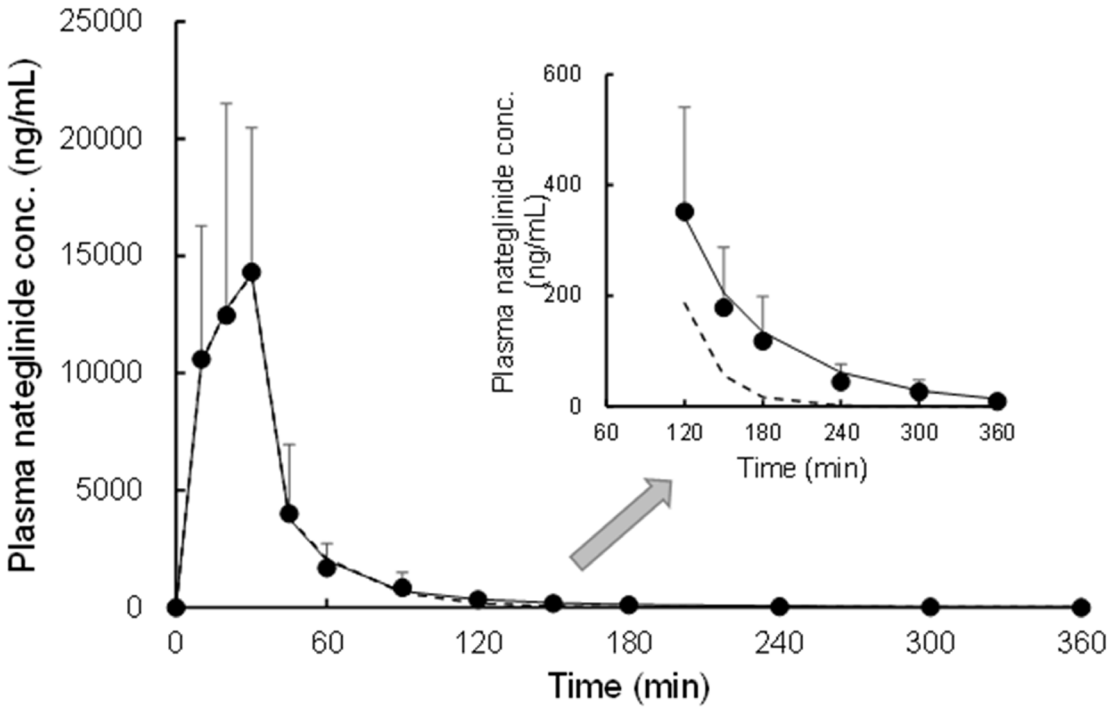

Figure 2: Fitted and observed plasma concentrations of nateglinide after intravenous infusion to GK rats. **Note:** Inset figure shows a magnification of the figure at the lower concentration range. Fitted curves were obtained according to the two (broken line) and three (solid line) compartment PK models. Each point represents the mean+Standard Deviation (SD) of the data obtained from 5 experiments.

Table 1 summarizes the PK parameters calculated by non-compartmental analysis. The CL_{tot}, $t_{1/2}$, and V_{dss} were 7.19 ml/min, 67.6 min, and 777 ml, respectively. The MRT was 21.2 min we analyzed the nateglinide PK model by adapting the data to 2 and 3 compartment PK models (Figure 1). The fitting curves profiles (Figure 2) in the high-concentration range were nearly identical for both models. However, the results of both models differed when the plasma concentration decreased (Figure 2). The profile of the 2-compartment model fitting was underestimated, whereas that of the 3-compartment model almost fit the data (Table 1).

Table 2 lists the PK parameters obtained by fitting the PK models. Akaike's Information Criterion (AIC) values for both models were similar. The half-lives of phase α ($t_{1/2\alpha}$) and phase β ($t_{1/2\beta}$) in the 2-compartment model analysis were 0.150 and 17.2 min, respectively. In contrast, the $t_{1/2\alpha}$, $t_{1/2\beta}$, and half-life of the phase γ ($t_{1/2\gamma}$) in the 3-compartment model were 0.109, 13.7, and 67.2 min, respectively. The $t_{1/2\gamma}$ in the 3-compartment model was similar to the terminal $t_{1/2}$ calculated by non-compartmental analysis. Although the 3-compartment PK model was fitted to all plasma concentration ranges at the 10 mg/kg dose, six PK parameters had to be calculated using the 12-plasma concentration-time data. Sensitivity analyses of the calculated PK parameters by two- and three-compartment PK models were performed to confirm their effects on plasma concentration profiles. The results are illustrated in Supplementary Figure 1. While k_{12} and k_{21} exhibited relatively low sensitivity, and k_{13} and k_{31} showed low sensitivity to the plasma concentration profiles, other parameters significantly influenced their profiles. These parameters represent the transition process, and their values are smaller than k_{10}, except for k_{12} (Table 2).

PK-PD analysis of nateglinide

Figure 3 illustrates the insulin and glucose plasma concentration-time profiles (Figure 3). After initiating nateglinide infusion, the plasma insulin level rapidly increased and the time to reach its maximum was 30 min. After terminating the infusion, plasma insulin levels decreased, which was similar to the nateglinide profile. In contrast, the plasma glucose concentration decreased more slowly than the increase in insulin, and the minimum concentration of glucose was reached at 60-90 min. Table 3 lists the fitting parameters of the PK-PD models. The fitting results obtained using the 2 and 3 compartment PK models were almost identical. Sensitivity analyses of PD parameters were conducted to confirm their effects on PD profiles. The results are demonstrated in Supplementary Figure 2. The sensitivity of γ_G, for the effect from insulin to glucose, was low. Other parameters significantly influenced their PD profiles (Table 3).

Figure 4 illustrates the relationships between nateglinide and insulin (A) and between insulin and glucose (B). Plasma nateglinide and insulin concentrations were directly correlated (Figure 4A). When the nateglinide plasma concentration was increased or decreased, the change in insulin levels was almost proportional to the plasma nateglinide concentration, and no hysteresis was observed. However, the relationship between the plasma insulin and glucose concentrations was different (Figure 4B). A decrease in glucose level was observed after an increase in plasma insulin concentration, and hysteresis with a delayed effect was observed. In other words, plasma insulin rapidly responded to an increase in nateglinide concentration, and insulin concentration increased. However, it took some time for the plasma glucose concentration to decrease after the insulin concentration increased. Therefore, the expression patterns of the insulin-increasing effects of nateglinide and those of the glucose-lowering effects of insulin were different (Figure 4).

Table 1: Pharmacokinetic parameters of nateglinide after intravenous infusion in GK rats.

PK parameters	AUC (mg × min/ml)	$t_{1/2}$ (min)	CL_{tot} (ml/min)	V_{dss} (ml)	MRT (min)
Mean	570	67.6	7.19	777	21.2
SD	299	21.4	4.86	749	3.0

Note: Data represent the mean ± Standard Deviation (SD) of five experiments; PK: Pharmacokinetics; AUC: Area Under The Curve; $t_{1/2}$: terminal elimination half-life; CL_{tot}: Total body clearance; V_{dss}: Distribution volume at the steady-state; MRT: Mean Residence Times.

Table 2: Pharmacokinetic parameters of nateglinide in rats calculated by two and three compartment pharmacokinetic models.

PK parameters		PK model	
		2-compartment model	3-compartment model
V_1	ml	2.96	1.93
k_{10}	1/min	1.95	2.87
k_{12}	1/min	2.61	4.39
k_{21}	1/min	0.0953	0.122
k_{13}	1/min		0.357
k_{31}	1/min		0.0147
AIC		180.6	180.8

Note: The PK models are illustrated in Figure 1. Each value was calculated using the mean data obtained from 5 experiments. PK: Pharmacokinetics; V_1: Distribution volume of the central compartment; k_{12}, k_{21}, k_{13}, k_{31}, and k_{10}, first-order rate constants for the pharmacokinetic processes; AIC: Akaike's Information Criterion.

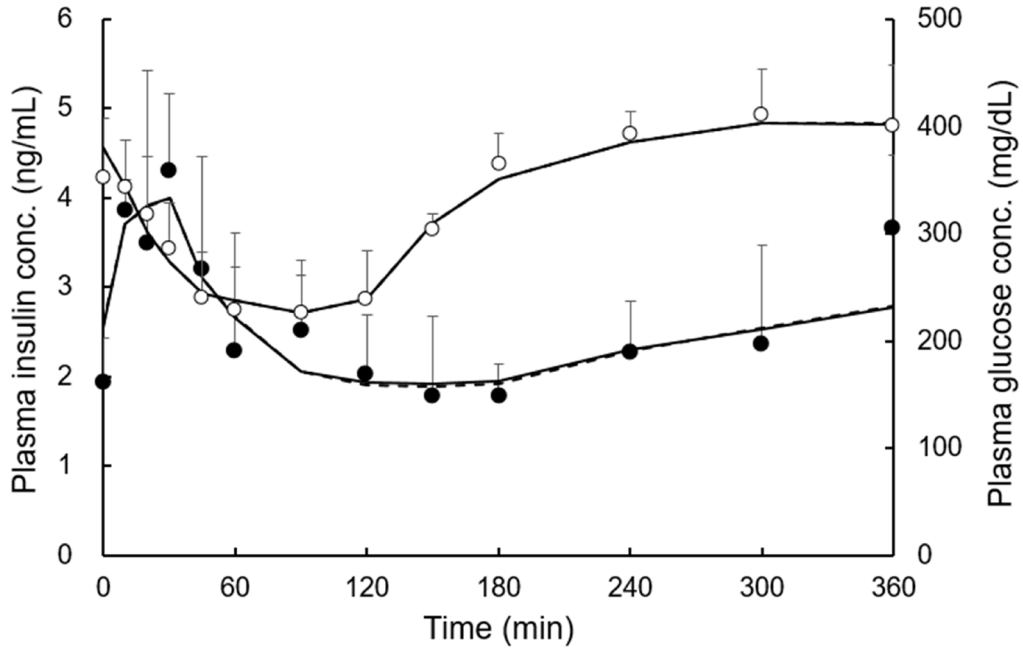

Figure 3: Pharmacodynamic responses with respect to time after intravenous infusion of nateglinide to GK rats. **Note:** Closed and open circles represent observed plasma insulin and glucose concentrations, respectively. Each point represents the mean+Standard Deviation (SD) of data obtained from 6 experiments. Fitted curves were obtained according to the two (broken line) and three (solid line)-compartment PK models shown in Figure 1.

Table 3: Pharmacodynamic parameters of nateglinide in rats.

PK model	Indirect response model					
	Nateglinide → insulin			Insulin → glucose		
2-compartment model	K_{inI}	ng/ml/min	0.433	K_{inG}	mg/dl/min	8.21
	k_{outI}	1/min	0.168	k_{outG}	1/min	0.0216
	E_{maxI}		89.0	I_{maxG}		0.473
	EC_{50I}	ng/ml	6358407	IC_{50G}	ng/ml	2.71
	g_I		0.759	g_G		460
	AIC		24.1	AIC		112.7
3-compartment model	K_{inI}	ng/ml/min	0.452	K_{inG}	mg/dl/min	8.25
	k_{outI}	1/min	0.178	k_{outG}	1/min	0.0217
	E_{maxI}		128	I_{maxG}		0.472
	EC_{50I}	ng/ml	14336904	IC_{50G}	ng/ml	2.73
	g_I		0.719	g_G		461
	AIC		24.0	AIC		112.6

Note: Each value was calculated using the mean data obtained from 6 experiments. The PK-PD model is illustrated in Figure 1. PK parameters employed in the PK/PD analysis were listed in Table 2. The subscripts I and G indicate the values for insulin and glucose, respectively. PK: Pharmacokinetics; K_{in} and k_{out}, zero- and first-order rate constants related to the formation and degradation of insulin and glucose; E_{max} and I_{max}, the maximum drug effect; EC_{50} and IC_{50}, drug concentration at half-maximum effect; γ: Hill constant; AIC: Akaike's Information Criterion.

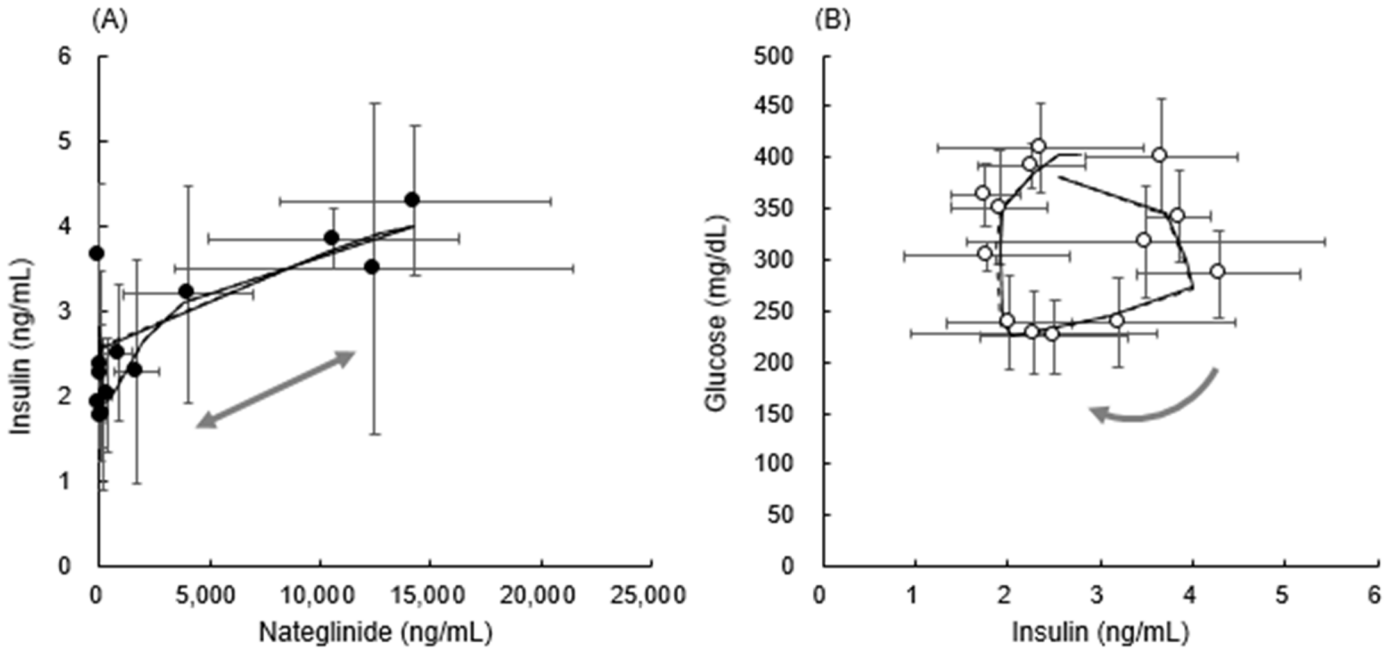

Figure 4: Relationships among plasma nateglinide, insulin, and glucose concentrations after nateglinide intravenous infusion to GK rats. Relationships are between plasma nateglinide and insulin concentration (A), and between plasma insulin and glucose concentration (B). **Note**: Symbols represent data obtained from experiments, and lines represent the model-fitting results shown in Figure 1 for the two (broken line) and three (solid line) compartment Pharmacokinetic (PK) models. Each observed point represents the mean ± Standard Deviation (SD) of data obtained from five or six experiments.

DISCUSSION

Plasma concentrations were measured and considered an indicator of its effect since the PK of a drug is closely related to its effects/side effects. However, the PK of a drug is not proportional to its efficacy. Several factors are involved in the manifestation of these effects. Therefore, using PK-PD analysis, explaining the transition in effects/side effects in relation to PK is possible [1-5]. Herein, we investigated the relationships between the time profiles of plasma nateglinide and both insulin and glucose concentrations in GK rats, a type 2 diabetes model. Time profiles of the insulin and glucose concentration groups were evaluated to determine the effects of nateglinide. This study was conducted using iv infusion, excluding the absorption process. Nateglinide is rapidly absorbed in the small intestine of rats after oral administration; its plasma concentration reaches its maximum 30 min after administration and the estimated bioavailability is 45% [17].

Nateglinide is highly distributed in the liver and kidneys of rats early after administration and is mainly metabolized in the liver [18]. The P-450 isoform involved in nateglinide metabolism is mainly CYP2C9 and the pharmacological effect of any metabolite is less than that of the parent compound. The effect of the main metabolite is approximately one-sixth that of nateglinide [19]. Nateglinide is entirely eliminated through urine and feces (mainly excretion to bile) within 168 h after administration. Approximately 20% of nateglinide excreted in bile is reabsorbed from the small intestine and enterohepatic circulation is observed [17]. Additionally, nateglinide is highly bound to plasma protein (>98%), primarily to albumin [20]. In the present study, the plasma concentration of nateglinide rapidly decreased at 120 min after initiating infusion, followed by a terminal elimination phase with a t1/2 of approximately 68 min.

GK rats were used as the pathological models in our experiments. Compared with normal rats, the plasma concentration of nateglinide was higher and CL_{tot} was lower in GK rats [21]. Similar results were obtained in our investigation of the PK of glimepiride, a type 2 antidiabetes agent [9]. Plasma total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride were previously found to be substantially higher in GK rats than in a non-diabetic control group [22]. These properties are hypothesized to cause higher plasma concentrations of lipophilic drugs, such as glimepiride and nateglinide [23]. In the human PK of nateglinide, elimination from the plasma is rapid, similar to the findings in rats, with an elimination half-life of approximately 3 h [24].

Here, the PK parameters of nateglinide were calculated by model fitting analysis using the mean plasma concentration-time data. Next, PK-PD analysis was performed using the resultant PK parameters. The PD parameters were calculated to fit the PDs in sequence more accurately. The PK analysis of nateglinide was performed to adapt the data to 2 and 3 compartment models. AIC values, which are indices of fit, were similar.

The 3-compartment model was found to fit better with the measured values down to the low-concentration range than the 2-compartment model. However, low plasma nateglinide concentrations had only minor effects. The PK parameters of the first-order rate constants between the central and 2nd compartments were similar in the two PK models. Plasma nateglinide concentration rapidly decreased to one-tenth of that at the end of the infusion within 30 min. The rate constants calculated from the central compartment were larger than those in our previous investigation of glimepiride [9]. The rapid plasma elimination of nateglinide possibly results in short-term insulin secretion. Compared with the parameters obtained from both compartment analyses, V_1 and the rate constants between the central and 2nd compartments (k_{12} and k_{21}) were similar. The terminal phase of the obtained profile demonstrated a distribution in the 3rd compartment. However, our results indicate that this phase did not substantially alter the effects of nateglinide.

The fitted plasma insulin and glucose concentration profiles were well-fitted to the observed data and were largely fitted to the two models. The PK-PD model, based on the pharmacological mechanism of nateglinide, explained the observed values well. PK model candidates are preferably concise and include the necessary conditions and processes. In the present study, the fitted PK profile was closer to the actual measurement values in the 3-compartment model than in the 2-component model. However, the plasma insulin and glucose profiles of nateglinide were similar. Therefore, in the PK-PD analysis of nateglinide, a 2-compartment model was considered sufficient. This PK-PD model described the observed plasma nateglinide, insulin, and glucose concentration-time profiles. In addition, the relationship between plasma nateglinide and insulin concentrations differed from that between plasma insulin and glucose concentrations. Plasma insulin levels began to rapidly increase after nateglinide infusion and insulin levels simultaneously decreased with a decrease in nateglinide concentration. In contrast, hysteresis with a time lag was observed for the effect of insulin on glucose levels. It takes time for an increase in insulin concentration to cause a decrease in glucose concentration. As we conducted this analysis using rats, modeling was performed using a limited amount of data. When applying this model to humans, PK-PD parameters would be obtained more accurately by obtaining an appropriate number of measurements according to the number of parameters. Furthermore, future studies should incorporate factors representing the degree of diabetes.

Nateglinide binds to Sulfonylurea (SU) receptors on the pancreatic β-cell membrane, shutting off ATP-sensitive K^+ channels and causing membrane depolarization. Consequently, L-type Ca^{2+} channels are opened and the intracellular Ca^{2+} concentration increases owing to CA^{2+} influx from outside the cell. This elevation is thought to cause exocytosis of insulin secretory granules [12-14].

Type 2 diabetes is a heterogeneous disorder characterized by defects in the early phase of insulin secretion after meals and insulin resistance at its early stage. Nateglinide, an insulin secretagogue, elicits acute insulin release, improves excessive excursion of postprandial glucose by augmenting early insulin secretion after a meal, and reduces postprandial hyperglycemia in patients [25]. Hyperglycemia in patients with type 2 diabetes mellitus can be due to the following: (i) decreased glucose uptake into the skeletal muscle due to peripheral insulin resistance; (ii) increased hepatic glucose production (mainly gluconeogenesis) due to hepatic insulin resistance; and (iii) decreased insulin secretion due to β-cell exhaustion, genetic causes, or glucotoxicity [26,27]. Therefore, drugs that ameliorate one or more of these defects can be used in treating type 2 diabetes mellitus. Sulfonylurea drugs, including glimepiride, gliclazide, and tolbutamide, stimulate insulin secretion from the β-cells. Nateglinide stimulates insulin secretion by the same mechanism as sulfonylureas but has a more rapid onset and shorter duration of action [28,29].

Ikenoue et al. reported that simultaneously measuring plasma insulin and glucose levels after orally administering nateglinide in normal dogs revealed rapid-onset and short-term insulin secretion, and a hypoglycemic effect [13]. The PK profile of nateglinide was consistent with the changes in plasma glucose and insulin levels. Plasma glucose and insulin levels largely returned to normal levels after 6 and 2 h, respectively. These rapid effects differed from those of glibenclamide, gliclazide, and torubutamide. In contrast, a time lag was observed in the relationship between plasma concentration profiles of insulin and glucose in old Zucker insulin-resistant model rats [12]. Moreover, a time lag between plasma insulin increase and glucose decrease was observed in patients with type 2 diabetes [11]. This result is similar to our findings. Herein, the plasma insulin level increased and subsequently decreased with nateglinide plasma concentration, although the change in plasma glucose level took time in the GK rats. Nateglinide ameliorates insulin resistance and insulin secretion defects in patients with type 2 diabetes [30]. One reason for the difference in these results may be the difference in the responsiveness to insulin of the experimental animals used.

CONCLUSION

Herein, we investigated the relationship between the time profiles of plasma nateglinide, insulin, and glucose concentrations in a type 2 diabetes model (GK rats) using PK-PD model analysis based on the pharmacological mechanism. The expression patterns of the insulin-increasing effects of nateglinide and glucose-lowering effects of insulin were different. Our results confirm that model analysis and results from animal experiments can be used to predict the PK and effect profiles of nateglinide in humans by considering differences in PK and PD between animals and humans. Additionally, estimating the PK and effect of the drug on changes in pathological conditions and drug interactions is possible in patients by adapting the parameters.

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DECLARATION OF INTEREST

The authors report there are no competing interests to declare.

CONFLICT OF INTEREST

The authors declare no conflicts of interest concerning this study.

AUTHOR CONTRIBUTIONS

Akiko Kiriyama: Conceptualization, data curation, formal analysis, original draft, and Writing-review and editing. Shunsuke Kimura: Data curation, formal analysis. Shugo Yamashita: Data curation, formal analysis.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

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