BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **31**: 443–449 (2010)
Published online 31 August 2010 in Wiley Online Library
(wileyonlinelibrary.com). **DOI**: 10.1002/bdd.724

SHORT COMMUNICATION

Effect of Fluvastatin, Lovastatin, Nifedipine and Verapamil on the Systemic Exposure of Nateglinide in Rabbits

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ABSTRACT: A diabetic patient may suffer simultaneously from cardiovascular disease; thus, lipid-lowering or anti-hypertensive agents could be given together with nateglinide. The pharmacokinetics of nateglinide were investigated in the presence and absence of HMG-CoA reductase inhibitors (fluvastatin, lovastatin) and calcium channel blockers (verapamil, nifedipine) in rabbits. A pharmacokinetic modeling approach was used to quantify the effects of the drugs that significantly influenced the pharmacokinetics of nateglinide. Fluvastatin and nifedipine shifted the time course of serum nateglinide concentrations upwards; there was no significant change with verapamil or lovastatin. The C_{max} and AUC_{inf} increased 1.5- ($p<0.05$) and 1.3-fold in the presence of fluvastatin and 1.8- ($p<0.01$) and 2.4-fold ($p<0.01$) in the presence of nifedipine, respectively. In a simultaneous nonlinear regression, fluvastatin and nifedipine decreased the elimination rate constant, by 76% and 32%, respectively. Fluvastatin and nifedipine increased the systemic exposure of nateglinide in rabbits, probably due to their inhibitory action on the metabolism of nateglinide by CYP2C5 (human CYP2C9). The concomitant use of fluvastatin and/or nifedipine with nateglinide is quite likely; therefore, the clinical consequences of long-term treatments must be considered.

Key words: nateglinide; fluvastatin; lovastatin; nifedipine; verapamil; rabbits

Introduction

Nateglinide is a popular anti-diabetic agent used for the treatment of non-insulin-dependent diabetes mellitus. This drug was developed to improve the undesired side-effects associated with sulfonylurea-type agents, such as hypoglycemia due to sustained insulin release, and impaired glucose tolerance, as a result of the exhaustion of the β-cells in the pancreatic islets during long-term treatment [1]. Nateglinide has been used for meal-time glucose control, because it binds sulfonylurea receptors and β-cell K_{ATP} channels, resulting in a rapid onset and short insulin response [2].

Nateglinide is known to be transformed in the intestine and liver by CYP2C9 and CYP3A4 [3]. The effects of 18 drugs on the biotransformation of nateglinide to its major metabolite were examined in human liver microsomes; these agents can be prescribed concomitantly with nateglinide [4]. Miconazole showed a strong inhibition of nateglinide metabolism, followed by nifedipine, rosiglitazone, pioglitazone, gemfibrozil and fluconazole.

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Received 3 June 2010
Revised 6 July 2010
Accepted 30 July 2010

There are few studies describing food–and drug–nateglinide interactions *in vivo*. It has been reported that nateglinide and elevated meal-time glucose concentrations had a synergistic effect on the secretion of insulin, when compared with the fasting condition [5], and that rifampicin reduced nateglinide the area under the plasma concentration–time curve (*AUC*), by 25% [6]. In contrast, diclofenac did not alter the pharmacokinetics of nateglinide in healthy subjects [7], and there was no pharmacokinetic or pharmacodynamic interaction between nateglinide and the anticoagulants warfarin [8] and acenocoumarol [9] in healthy volunteers.

Because a diabetic patient may suffer simultaneously from cardiovascular disease, lipid-lowering or anti-hypertensive agents could be administered with nateglinide. The pharmacokinetics of nateglinide were investigated in the presence and absence of HMG-CoA reductase inhibitors (fluvastatin, lovastatin) and calcium channel blockers (verapamil, nifedipine) in rabbits. A pharmacokinetic modeling approach was used to quantify the effect of the drugs that had a significant influence on the pharmacokinetics of nateglinide.

Methods

Materials

Nateglinide, fluvastatin, lovastatin, verapamil, nifedipine and phenacetin were purchased from Sigma-Aldrich Chemical Co. (Seoul, Korea). Methanol and acetonitrile were used for high-performance liquid chromatography (HPLC) analysis. Other reagents were of analytical grade.

Pharmacokinetic studies

New Zealand White male rabbits, weighing 2.0–2.5 kg, were obtained from Samtako Bio Co., Ltd (Osan, Korea). The animals were fasted overnight, and until the end of the experiment, but were allowed water *ad libitum*. Rabbits were divided into five groups of six animals each. All drugs were suspended in 0.5% carboxymethylcellulose solution. Nateglinide (30 mg/kg) was given to the control group, and fluvastatin (3 mg/kg), lovastatin (3 mg/kg), verapamil (20 mg/kg) or nifedipine (5 mg/kg) were administered with nateglinide to the treatment groups. Serum samples (0.7 ml) were collected from the marginal ear vein before, and 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 6 h and 8 h after drug administration, and were analysed by HPLC. All studies were carried out according to the Principles for Biomedical Research Involving Animals, developed by the Council for International Organizations of Medical Sciences.

Determination of nateglinide

Nateglinide in rabbit serum was determined by a previously reported method [10] with slight modifications. Phenacetin (600 μl; internal standard, 50 μg/ml in acetonitrile) was added to serum (300 μl) and mixed vigorously for 3 min. After centrifugation (13000 rpm, 10 min) 300 μl of the supernatant was evaporated to dryness at 50°C under a nitrogen stream. The residue was reconstituted in 120 μl of mobile phase; 50 μl was injected into the HPLC system.

The chromatographic system consisted of a pump (LC-10AD), an automatic injector (SIL-10A) and a UV detector set at 210 nm (SPD-10A; Shimadzu Scientific Instruments, Japan). An ODS column (μBondapak C18, 3.9 × 300 mm, 10 μm; Waters, USA) was eluted with a mixture of 0.1 M potassium hydrogen phosphate solution (pH 6.6, adjusted with 5 M hydrochloric acid), methanol and acetonitrile (35:20:4, v/v/v) at a flow rate of 1 ml/min. A calibration curve was prepared, based on the peak area ratio of nateglinide to the internal standard corresponding to the concentrations in spiked serum samples.

Model-independent analysis

A non-compartmental approach was used for pharmacokinetic data analysis. The pharmacokinetic parameters were determined using WinNonlin® (ver. 2.1; Pharsight Corp., Mountain View, CA, USA). The area under the serum drug concentration–time curve from time zero to infinity (AUC_{inf}) was obtained by the trapezoidal rule and extrapolation using an elimination rate constant. The maximum serum concentration (C_{max}) and the time (T_{max}) to reach C_{max} were determined directly from the individual drug

DOI: 10.1002/bdd

concentration against time curves. The terminal elimination rate constant (k_e) was estimated by linear regression from the points describing the elimination phase on a log-linear plot. The half-life ($t_{1/2}$) was calculated by $0.693/k_e$, and the total clearance (CL) was calculated by dose/AUC_{inf}.

Pharmacokinetic parameters of nateglinide following oral administration in the presence and absence of the lipid-lowering or anti-hypertensive agents were compared using Student's t-test. A value of $p<0.05$ was deemed to indicate statistical significance.

Model-dependent analysis

Statistically significant data sets were further analysed using a pharmacokinetic modeling approach. Model identifiability is pivotal in the modeling process; therefore, uncertainties associated with the parameters of the model must be addressed. Because many parameter values in models are dependent on raw data, models may produce different parameter sets, even though the data are obtained following treatments in the same species of animals. This problem can be overcome using simultaneous nonlinear regression (SNLR) [11,12], where the regression process is conducted for different experiments simultaneously, and the modeling function shares parameters that are independent of the specific experimental conditions. Simultaneous nonlinear regression can be successful when complete data sets are obtained from experiments performed in the presence and absence of concomitantly administered drugs. In this study, SNLR was performed with average data values (six rabbits in each group in the presence and absence of fluvastatin or nifedipine).

Simultaneous nonlinear regression analysis of the serum concentration–time curves obtained using a two-compartment model with first-order absorption and elimination that reflected the disposition kinetics of nateglinide, was performed (Figure 1). Models were constructed as a series of differential equations that were solved numerically and fitted to the data with the ADAPT II software package (Biomedical Simulation Resource, Los Angeles, CA, USA) [13]. Data fitting was performed by means of a maximum likelihood estimation using the assumption that

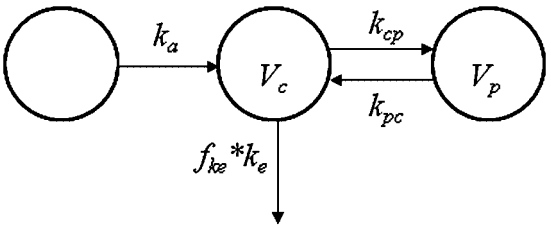

Figure 1. Final model structure

the standard deviation of the measurement error is a linear function of the measured quantity. The model equations were identical up to the factors (f) characterising selected pharmacokinetic parameters (P) in the presence of the other drugs. The factors accounted for potential changes in P that resulted from the treatments (model P was replaced by $f*P$ in the model of co-administration with the other drugs). All possible combinations of f were tested to describe the effect of the co-administration of lipid-lowering or anti-hypertensive drugs by a minimum number of f. The likelihood ratio test was performed to evaluate the statistical significance of model improvement by f and additional P [11]. The differential equations describing mass changes in the amounts of nateglinide in the presence and absence of the other drugs are given by Equations (1–3):

$$dx_1/dt = -(f_{ke}k_e + k_{cp})x_1 + k_a x_3 + k_{pc}x_2 \quad (1)$$

$$dx_2/dt = k_{cp}x_1 - k_{pc}x_2 \quad (2)$$

$$dx_3/dt = -k_a x_3 \quad (3)$$

First order rate constants describing absorption, elimination and inter-compartmental transport are denoted by k_a, k_e and k_{ij}, respectively. Subscripts c and p indicate central and peripheral, respectively.

The following information provided by ADAPT II was used to evaluate the goodness-of-fit and the quality of parameter estimates: coefficients of variation of parameter estimates (CVs), parameter correlation matrix, sum of squares of residuals, visual examination of the distribution of residuals and the Akaike information criterion. As criteria for evaluating the numerical identifiability of estimates, CV < 0.5

DOI: 10.1002/bdd

and a correlation coefficient threshold of 0.9 were used.

Results

Model-independent analysis

Figure 2 shows the mean nateglinide concentrations in serum following oral administration in the presence and absence of fluvastatin, lovastatin, nifedipine or verapamil. Model-independent pharmacokinetic parameters are listed in Table 1. When administered alone, nateglinide reached a C_{max} of 21.7 ± 1.6 mg/l at 0.9 h, and decayed bi-exponentially; there was a relatively fast decline up to 2 h, and then a slow decay with a terminal half-life of 4.4 h. The AUC_{inf} and total clearance (CL) were 96.2 ± 35.8 mg · h/l and 0.37 ± 0.19 l/h/kg, respectively.

Lovastatin and verapamil did not affect the time course of serum nateglinide concentrations, but it was shifted upwards by fluvastatin and nifedipine. The C_{max} and AUC_{inf} were increased 1.5- ($p < 0.05$) and 1.3-fold in the presence of fluvastatin, and 1.8- ($p < 0.01$) and 2.4-fold ($p < 0.01$) in the presence of nifedipine, respectively. The terminal half-life of nateglinide was increased 1.3- and 1.6-fold ($p < 0.05$) by fluvastatin and nifedipine, respectively. Fluvastatin and nifedipine decreased the clearance of nateglinide by 25% (not significant) and 62% ($p < 0.01$), respectively.

Accuracies for intra- and inter-day assay were higher than 92.6% and 90.5%, respectively. The coefficients of variation of assay were less than 6.5% for intra-day assay and 8.6% for inter-day assay. The limit of quantitation of nateglinide was 20 ng/ml.

Pharmacokinetic modeling

Fluvastatin and nifedipine caused a significant increase in the systemic exposure of nateglinide; thus, further analysis using a compartmental modeling approach was performed. Figure 3

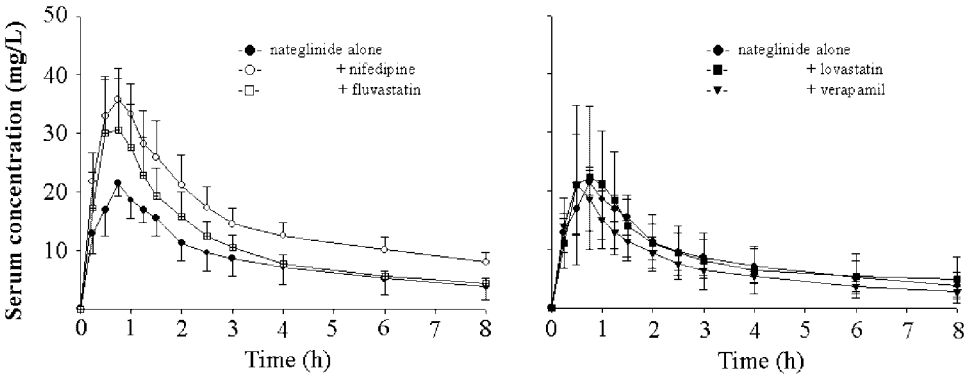

Figure 2. Time courses of serum nateglinide concentrations following oral nateglinide (30 mg/kg) administration in the presence and absence of fluvastatin (3 mg/kg), nifedipine (5 mg/kg), lovastatin (3 mg/kg) or verapamil (20 mg/kg) (mean ± SD; $n = 6$)

Table 1. Pharmacokinetic parameters of nateglinide following oral administration in the presence and absence of fluvastatin, lovastatin, nifedipine or verapamil in rabbits

Parameter	Nateglinide	Drug concomitantly administered			
		Fluvastatin	Lovastatin	Nifedipine	Nifedipine
C_{max} (mg/l)	21.7 ± 1.6	33.4 ± 6.9[a]	25.1 ± 11.9	39.7 ± 13.0[b]	22.2 ± 8.4
T_{max} (h)	0.9 ± 0.3	0.7 ± 0.2	0.8 ± 0.3	0.9 ± 0.4	0.6 ± 0.3
AUC_{inf} (mgh/l)	96.2 ± 35.8	126.5 ± 23.1	115.8 ± 35.1	229.1 ± 33.5[b]	87.8 ± 19.3
k_e (h^{-1})	0.22 ± 0.18	0.14 ± 0.06	0.19 ± 0.08	0.10 ± 0.02[a]	0.24 ± 0.12
$t_{1/2}$ (h)	4.4 ± 2.1	5.9 ± 3.1	3.8 ± 2.3	7.1 ± 1.3[a]	3.9 ± 1.7
CL (l/h/kg)	0.37 ± 0.19	0.28 ± 0.12	0.32 ± 0.15	0.14 ± 0.05[b]	0.42 ± 0.09

Each value represents mean ± SD ($n = 5$). [a]$p < 0.05$, [b]$p < 0.01$ compared with control.

DOI: 10.1002/bdd

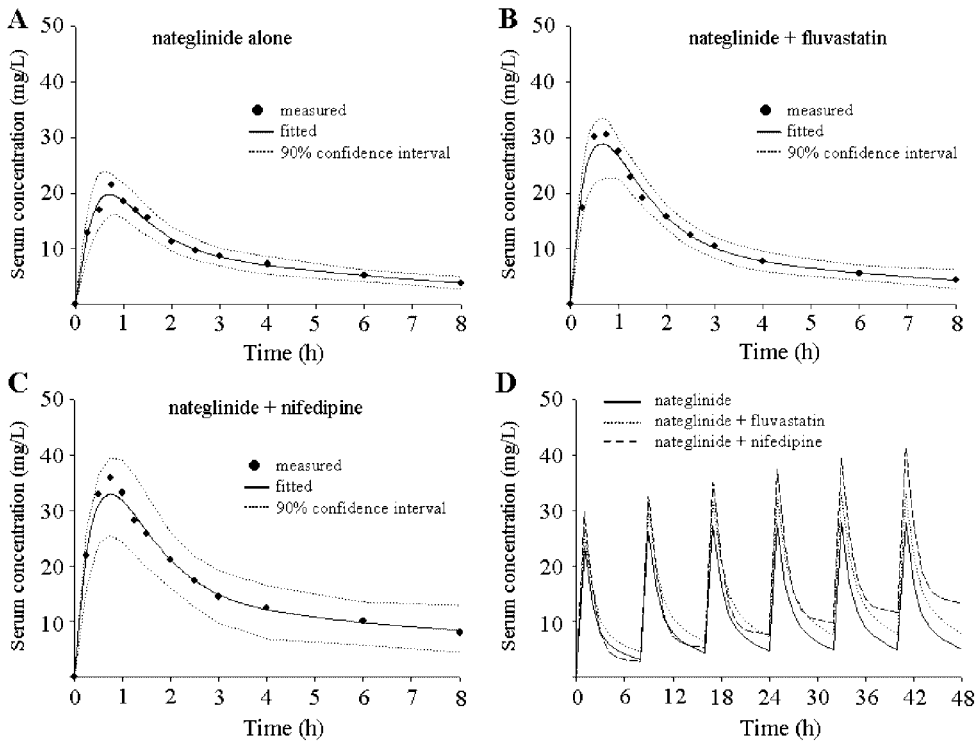

Figure 3. Simultaneous fit to the average serum concentrations of nateglinide following oral administration of nateglinide alone (A) or together with fluvastatin (B) or nifedipine (C). (D) The predicted time course of serum nateglinide concentrations following repeated oral administration in the presence and absence of fluvastatin or nifedipine

shows the simultaneous fits (solid lines) of average nateglinide serum concentration–time profiles in the presence and absence of fluvastatin and nifedipine; the model and the measured data are in agreement. The final parameter estimates obtained from the simultaneous nonlinear regression are listed in Table 2.

Fluvastatin and nifedipine caused a decrease in the elimination rate constant by 76% and 32%, (a decrease in k_e by factors $f_{ke,}$ 0.76 and 0.32, in the presence of fluvastatin and nifedipine), respectively. This factor completely described the effect of the two drugs on the pharmacokinetics of nateglinide because all the data were fit simultaneously by a single set of parameter values; the other parameters were shared to fit the three data sets. Asymptotic coefficients of variation for the parameter estimates were less than 26%, except for the distribution rate constant from the peripheral to the central compartment. Correlation coefficients were less than 0.85, indicating that each parameter was independently estimated.

Table 2. Model parameter estimates obtained from the simultaneous nonlinear regression for the pharmacokinetics of nateglinide in the presence and absence of fluvastatin or nifedipine in rabbits

Parameter[a]	Estimate	CV (%)[b]
k_a (h^{-1})	0.72	18.0
k_e (h^{-1})	1.60	19.2
k_{cp} (h^{-1})	3.13	16.4
k_{pc} (h^{-1})	0.11	45.9
V (l)	0.42	
$fk_{e,\ flu}$	0.76	9.5
$fk_{e,\ nif}$	0.32	25.8

[a] k_a, absorption rate constant; V (volume of distribution of central compartment); k_e, elimination rate constant; k_{ij}, inter-compartmental distribution rate constants from i to j; c, central compartment; p, peripheral compartment; $fk_{e,flu}$, $fk_{e,nif}$, additional parameter in the model equations accounted for the effect of fluvastatin or nifedipine, respectively (e.g. $k_{e,flu} = fk_{e,flu} \times k_e$).
[b] Asymptotic coefficient of variation.

Figure 3D represents the predicted time course of serum nateglinide concentrations following oral administration in the presence and absence of fluvastatin and nifedipine.

DOI: 10.1002/bdd

Discussion

To our knowledge, this is the first reported study to directly demonstrate the drug–drug interactions between nateglinide and fluvastatin, lovastatin, verapamil, or nifedipine *in vivo*. These results are of clinical significance when considering the treatment of diabetic patients who concomitantly have hyperlipidemia or hypertension. Fluvastatin and nifedipine administration resulted in a marked increase in the systemic exposure of nateglinide; lovastatin and verapamil had no significant effect.

Nateglinide is metabolised primarily by CYP2C9 (70%) and secondarily by CYP3A4 (30%). Lovastatin, simvastatin and atorvastatin are biotransformed by CYP3A4. Fluvastatin is converted by CYP2C9 and is the only statin known to inhibit the metabolism of the CYP2C9 substrates S-warfarin, phenytoin and glyburide [3]. Thus, fluvastatin may have a more potent action on nateglinide in the systemic circulation than lovastatin. Furthermore, fluvastatin is a lipophilic statin, and has a bioavailability of 30%, which is much higher than that of lovastatin (5%) [14].

Nifedipine is a CYP3A4-selective substrate that alters nateglinide levels [15]; our results could not identify the mechanism(s) responsible for this. However, the effect of nifedipine and several other drugs, including verapamil, diltiazem and difedipine, on the metabolism of irbesartan by CYP2C9 has been investigated [16]. CYP2C9 is primarily responsible for the oxidation of irbesartan; CYP3A4 is rarely involved. Nifedipine was identified as a potent non-competitive inhibitor of irbesartan metabolism by CYP2C9. In contrast, verapamil and diltiazem did not exhibit an inhibitory effect on the formation of the irbesartan mono-hydroxy metabolite. Nifedipine also significantly inhibited the methylhydroxylation of tolbutamide, a probe drug for CYP2C9 [17].

Human CYP2C9 is known to be responsible for the metabolism of 15% drugs currently used in therapeutics. It shares more than 77% of sequence identity with rabbit CYP2C5 crystallised by Williams *et al*. [18]. Fluvastatin and nifedipine shifted the systemic exposure of nateglinide upwards, probably due to the inhibition of nateglinide metabolism by CYP2C5. The profiles of nateglinide metabolites in serum were not measured, as orally administered nateglinide is well absorbed (bioavailability, 72%), and unchanged nateglinide is the major circulating component in plasma [19]. Thus, the change in the time course of serum nateglinide concentrations should be enough to explain the interactions seen in the present study.

Model-dependent analysis was conducted to quantify the effect of nifedipine and fluvastatin on the time course of nateglinide serum concentrations. Uncertainties associated with the modeling process were addressed by analysing three data sets simultaneously, with sharing of parameters. However, as some parameters were closely related to each other (k_e, V), it was difficult to obtain optimal parameters independently. The volume of distribution of nateglinide in rabbits was 0.42 l. This was calculated by extrapolation on the basis of body weight; the volume of distribution of nateglinide is 10 l in humans, suggesting only a minimal distribution beyond the plasma volume [19]. Finally, a relatively narrow coefficient of variation was obtained for the final parameter estimates (except k_{pc}; Table 2).

The influence of nifedipine and fluvastatin was explained by a 0.76- and a 0.32-fold decrease, respectively, in the elimination rate constant. This represents the systemic decay of nateglinide, together with its conversion into metabolites. Other factors did not work on the model parameters to explain the change in the pharmacokinetics of nateglinide; this was confirmed using the likelihood ratio test. The simulation in Figure 3D showed concomitant administration of fluvastatin and nifedipineincreased the C_{max} of nateglinide by 22% and 54%, and the *AUC* by 34% and 77%, respectively, at steady state in rabbits.

The impact of pharmacokinetic changes in nateglinide metabolism on the pharmacodynamics of the drug must be taken into account. Rifampicin reduced nateglinide area under the plasma concentration–time curve (*AUC*) by 25% and decreased its half-life, but it did not significantly alter the blood glucose-lowering response to nateglinide administration [20]. Co-administration of gemfibrozil and itraconazole with nateglinide produced the same results

DOI: 10.1002/bdd

[21]. In these studies, the pharmacokinetic alterations did not have pharmacodynamic consequences, probably because nateglinide, in a 'therapeutic window' of plasma concentrations, saturates the β-cell K_{ATP} channels. Further investigation is needed to confirm the influence of long-term fluvastatin and/or nifedipine treatment on the glucose-control response of netaglinide in humans.

In conclusion, fluvastatin and nifedipine increased the systemic exposure of nateglinide in rabbits, probably due to an inhibitory action on CYP2C5 (human CYP2C9); lovastatin and verapamil did not. A modeling approach quantified the influence of these drugs on the pharmacokinetics of nateglinide. Concomitant use of fluvastatin and nifedipine with nateglinide is highly probable; the clinical consequences of long-term treatment must be considered.

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DOI: 10.1002/bdd