[UCI]I804:24011-200000234701

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칼슘채널차단제와 고지혈증치료제가 혈당강하제인 nateglinide의 약물동태에 미치는 영향

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이 연구의 목적은 nateglinide 의 약물동태에 고지혈증약 (gemfibrozil, lovastatin, flavastatin)과 칼슘채널차단제 (diltiazem, verapamil, nifedipine)가 미치는 영향을 살피기 위함이다. 칼슘채널차단제나 고지혈증약으로 전처리하거나 전처리없이 nateglinide(30mg/kg)를 경구투여하여 약물동태학적인 자료를 취득했다. Nifedipine 이나 diltiazem 과 병용투여한 집단의 경우, AUC 와 C_{max} 가 현저하게 증가했는데 nifedipine 과 병용한 집단의 경우 더욱 두드러졌다. 이는 cytochrome P450 과 2C9 저해제인 nifedipine 과 diltiazem 에 의해 nateglinide 의 대사가 저해되기 때문으로 보인다. Nateglinide 와 고지혈증약물들과 병용투여한 약물들중에서, gemfibrozil 이 명백하게 nateglinide 의 약물동태에 영향을 끼쳤다. nateglinide 의 AUC 와 Cmax 의 감소는, 겜피브라질에 의한 나테글리나이드의 단백결합을 나타내는 CL 가 현저히 증가했다는 것과 관련되어 있다. 그러므로

nifedipine, diltiazem 또는 gemfibrozil 과의 병용투여시에 , nateglinide 투여 환자들에게서 혈중농도변화를 주의 깊게 관찰하는 것이 필요할 것이다.

Abstract

Effects of calcium channel blockers and lipid-lowering agents on the pharmacokinetics of nateglinide, a novel hypoglycemic agent in Rabbit

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The present study aims to investigate the effects of calcium channel blockers (diltiazem, verapamil, nifedipine) and lipid lowering agents (gemfibrozil, fluvastatin, lovastatin) on the pharmacokinetics of nateglinide in Rabbit. Pharmacokinetic parameters were determined following an oral administration of nateglinide (30 mg/kg) to rabbits in the presence and absence of calcium channel blockers or lipid lowering agents. With co-administration with nifedipine and diltiazem, AUC and C_{max} increased significantly with more marked effect of nifedipine. This was attributed to the inhibition of metabolism of nateglinide by nifedipine or diltiazem, which is a cytochrome P450 3A4 and 2C9 inhibitor. Among lipid-lowering agents co-administered with nateglinide, gemfibrozil significantly affected the pharmacokinetics of nateglinide. The AUC and C_{max} of nateglinide decreased significantly with considerable increase of CL indicating the

enhanced metabolism of nateglinide in the presence of gemfibrozil. Therefore, close monitoring the pharmacokinetics of nateglinide may be required in the combination therapy of nateglinide with diltiazem, nifedipine or gemfibrozil.

Key Words : Nateglinide, Diltiazem, Verapamil, Nifedipine, Gemfibrozil, Fluvastatin, Lovastatin, Pharmacokinetics

Ⅰ. Introduction

The prevalence and medical and economic impact of type 2 diabetes mellitus is increasing. New agents have been developed that act primarily to reduce postprandial glucose excursions, which may be of particular significance now that postprandial glucose excursions are known to be correlated with cardiovascular morbidity and mortality.

Nateglinide [N-(*trans*-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] (Fig. 1) is a novel non-sulfonylurea oral hypoglycemic agent, which induces rapid insulin secretion by pancreatic β cells and thus suppress postprandial hyperglycemia in patients with type 2 diabetes. [1-4]. Nateglinide sensitizes beta-cells to ambient glucose, reducing the glucose concentration needed to stimulate insulin secretion. Administration of nateglinide 5-30 min before a meal results in a short-duration burst of insulin release that mimics the normal physiological cephalic phase of insulin secretion [5-7].

The pharmacokinetics of nateglinide are characterized by rapid absorption and elimination, with good (73%) bioavailability. After oral administration, nateglinide is rapidly absorbed and peak plasma concentrations are reached after 0.5-1.0 hr [8,9]. The elimination of this drug is fast, which an elimination half-life is approximately 1.4 hr [10]. Nateglinide is more rapidly absorbed when given 0-30 minutes prior to meal ingestion than if given during the meal. Nateglinide undergoes extensive metabolism, and less than 8% drug is excreted unchanged [11]. Previous studies reported that hepatic cytochrome P450 (CYP) isoenzymes such as CYP2C9 and CYP3A4 are involved in nateglinide metabolism [12,13].

Nateglinide pharmacokinetics are linear over the dose range 60-240 mg. No significant pharmacokinetic alterations occur in renally impaired patients, in the elderly, or in mildly hepatically impaired patients[14]. Nateglinide administered prior to meals stimulates rapid, short-lived insulin secretion in a dose-dependent manner, thus decreasing mealtime plasma glucose excursions. Its effects on insulin secretion are synergistic with those of a meal. With increasing nateglinide doses, the risk of hypoglycemia also increases, but its incidence is low. Even if a meal is missed, and the patient skips the dose of nateglinide (as recommended in the event of a missed meal), the incidence of subsequent hypoglycemia remains low compared with long-acting agents. The postprandial insulinotropic effects of nateglinide are more rapid than those of repaglinide and more rapid and greater than those of glibenclamide (glyburide), while producing less prolonged insulin exposure and less risk of delayed hypoglycemia [14] .

Diabetes is a common disease of metabolism associated with an increased incidence of coronary artery disease such as heart disease or stroke. Hypertension or hyperlipidemia has been known to be one of the main risk factors of coronary artery disease in patients with diabetes. Therefore, the possibility of concomitant use of hypoglycemic agents with anti-hypertensive drugs or lipid-lowering agents is very high. In this study, we investigated the effects of calcium channel blockers (diltiazem, verapamil, nifedipine) and lipid lowering agents (gemfibrozil, fluvastatin, lovastatin) on the pharmacokinetics of nateglinide.

Ⅱ. Methods

Animal Studies

New Zealand White male rabbits weighing 1.5-2.5 kg were obtained from Samtako Bio Co., Ltd (Osan, Korea). The rabbits were anesthetized with 1 mL/kg of ketamine hydrochloride (50mg/mL, Yuhan Corp., Seoul, Korea) and the right femoral artery was cannulated using a polyethylene tubes (0.58 mm i.d. × 0.96 mm o.d.; Naume Corp., Tokyo, Japan). After surgery, each animal was housed individually in cage. The animals fasted overnight until the end of the experiment but were allowed water ad libitum. Rats were then divided into nine groups, comprising 6 rats each. Group 1 was administered orally with a dose of 30 mg/kg of nateglinide. Group 2-7 was administered orally with nateglinide (30 mg/kg) 30 min after the administration of diltiazem (10 mg/kg), verapamil (20 mg/kg), nifedipine (5 mg/kg), gemfibrozil (150 mg/kg), lovastatin (3 mg/kg) and fluvastatin (3 mg/kg), respectively. Also, group 8-9 was administered orally with nifedipine or gemfibrozil at the same dose as the above every day for 4 days to induce liver CYP. On the 5th day, group 8-9 was administered orally with nateglinide (30 mg/kg) 30 min after the administration of nifedipine (5 mg/kg, pre-nifedipine) or gemfibrozil (150 mg/kg, pre-gemfibrozil). Serum samples (0.7 mL) were collected from the femoral artery cannula before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hr after drug administration and analyzed 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.

Nateglinide Assay

Slightly modified HPLC method of nateglinide was employed [15]. The nateglinide sample was assayed by high-performance liquid chromatography (HPLC) system. To 0.3-mL serum samples was added 300 μL of phenacetin (1000 μg/mL in acetonitrile), which was used as an internal standard (IS). To precipitate protein, 270 μL of acetonitrile was added to the samples and vortex-mixed for 5 min. After centrifugation of the mixture for 10 min at 13000 rpm, 300 μL of the supernatant was evaporated to dryness at 50 ºC under a stream of nitrogen gas. The residue was reconstituted with 120 μL of mobile phase and then 50 μL was injected directly into the HPLC system.

The chromatographic system was consisted of a pump (LC-10AD), an automatic injector (SIL-10A) and a UV detector (SPD-10A) (Shimadzu Scientific Instruments, Japan) set at 210 nm. An ODS column (μBondapak C18, 3.9 × 300 mm, 10 μm, Waters, USA) was eluted with a mixture of 0.1M potassium hydrogen phosphate solution, methanol and acetonitrile (350 : 200 : 40, v/v) (pH 6.6 adjusted with 5M hydrochloric acid) at a flow rate of 1 mL/min and at room temperature. A calibration curve was constructed based on peak area measurements.

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed using Kinetica-4.3 (InnaPhase Corp., Philadelphia, PA, USA). The area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal

method. The terminal elimination rate constant (λz) was estimated from the slope of the terminal phase of the log plasma concentration-time points fitted by the method of least-squares, and then the terminal elimination half-life ($T_{1/2}$) was calculated as 0.693/ λz. Additional estimated parameters using noncompartmental pharmacokinetic analysis were systemic plasma clearance (CL) and the volume of distribution (Vdss). Renal clearance (CL_R) was calculated as CL_R = Ae/AUC, where Ae (amount of unchanged drug eliminated in urine) and AUC are measured over the same time interval.

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Ⅲ. Results

The mean serum concentration versus time curves with and without concomitant calcium channel blockers are depicted in Fig. 3. The following pharmacokinetic parameters are described in Table 2. Among calcium channel blockers co-administered with nateglinide, nifedipine increased the $AUC_{0-\infty}$ and AUC_{0-8} significantly compared to nateglinide alone; those values were 201.8% ($P < 0.05$) and 180.7% ($P < 0.05$) of the respective control value. The C_{max} and half-life of nateglinide increased from 21.7 to 39.7 μg/mL ($P < 0.01$) and 4.4 to 7.1 hr ($P < 0.05$) by nifedipine, respectively. Diltiazem also increased C_{max} and AUC_{0-8} of nateglinide from 21.7 to 39.0 μg/mL ($P < 0.05$) and 68.7 to 91.8 μg · hr/mL ($P < 0.05$), respectively. The clearance of nateglinide was decreased significantly ($P < 0.05$) by the concomitant administration with nifedipine, possibly due to the decreased elimination rate. The pre-induction group by nifedipine increased AUC_{0-8}, $AUC_{0-\infty}$ and half-life significantly compared to control group. However, there was no significant difference in the pharmacokinetic parameters between nifedipine group and pre-induction nifedipine group. On the contrary, verapamil did not affect the pharmacokinetic profiles of nateglinide.

Among lipid-lowering agents, gemfibrozil decreased the $AUC_{0-\infty}$, AUC_{0-8} and C_{max} of nateglinide from 96.2 to 43.1 μg · hr/mL ($P < 0.05$), 68.7 to 30.8 μg · hr/mL ($P < 0.005$) and 21.7 to 10.3 μg/mL ($P < 0.0001$), respectively (Fig. 2, Table 1). The significantly increased CL by gemfibrozil was attributed to the increased Vz because half-life did not change.

Ⅳ. Discussion

The present results indicate that diltiazem and nifedipine can increase the plasma concentrations of nateglinide while gemfibrozil decreases them. Nateglinide has low lipophilicity and it has been suggested to be actively transported by an intestinal uptake transporter that has yet to be identified [16]. Whether or not nateglinide is a substrate for an efflux transporter, such as P-glycoprotein [17], is not known. From the systemic circulation, nateglinide is eliminated primarily via oxidative biotransformation [18]. CYP2C9 and CYP3A4 have been suggested to take part in the metabolism of nateglinide, with CYP 2C9 metabolizing it to a much greater extent than CYP 3A4 [18,19]. The biotransformation of nateglinide yields several metabolites, of which the dehydrogenated M7 metabolite seems to be as potent a blood glucose-lowering agent as the parent nateglinide [20]. However, all other metabolites appear to be much less active [20]. Total exposure to M7 is about 5% of that of nateglinide [18]. Because of its low lipophilicity, nateglinide may require active uptake from blood into the liver to become available for hepatic drug metabolism.

Even though all the calcium channel blockers employed in this study – diltiazem, nifedipine and verapamil - are known to be inhibitors of CYP3A4 and CYP2C9, they led to different pharmacokinetic results of nateglinide. As shown in Table 1, nifedipine increased the plasma concentrations of nateglinide the most markedly, while verapamil did not affect the concentrations of nateglinide. The significant increase of AUC and half-life by the addition of nifedipine was explained by the inhibition of nateglinide metabolism. Diltiazem also increased C_{max} and AUC_{0-8} of

nateglinide significantly. The exact mechanisms why those calcium channel blockers showed different results of nateglinide are required to be further investigated.

Gemfibrozil is a fibric acid derivative, which is used in the treatment of patients with lipid disorders [21]. A combined use of gemfibrozil and a statin can result in severe myopathy and rhabdomyolysis [22,23]. Recently, gemfibrozil has been found to elevate markedly plasma repaglinide, possibly inhibiting CYP-mediated metabolism of repaglinide. However, in this study, gemfibrozil rather reduced the plasma concentrations of nateglinide significantly as depicted in Fig. 2. This was probably thought that the concentrations of gemfibrozil did not reach high enough concentrations for a sufficient duration of time to substantially inhibit CYP2C9 activity. The reduced concentrations of nateglinide was attributed to the increased volume of distribution by co-administration of gemfibrozil. Nateglinide is extensively bound (99%) to serum proteins – mainly serum albumin and, to a lesser extent, alpha1-acid glycoprotein [24]. Gemfibrozil is also highly plasma protein bound (99%) [25]. Since nateglinide and gemfibrozil share a strong binding affinity for the same protein, the reduced concentrations of nateglinide with co-administration of gemfibrozil were attributable to the increased volume of distribution with the replacement of protein binding of nateglinide by gemfibrozil. In the pre-induction group by gemfibrozil, C_{max} and AUC increased compared to gemfibrozil group without pre-induction, even though it was not statistically significant, possibly due to the somewhat inhibition of CYP-mediated metabolism of nateglinide.

The other lipid-lowering agents used in this study, fluvastatin and lovastatin failed to reveal the significant increase of nateglinide concentrations even though

they have demonstrated inhibitory effects on CYP 2C9 *in vitro* and *in vivo* [26,27]. To confirm the results of this study, further clinical studies are required at the therapeutic dose levels with enough duration of therapy.

Ⅴ. Conclusion

The concomitant use of nifedipine or diltiazem with nateglinide significantly increases the serum concentrations of nateglinide, possibly due to the inhibition of nateglinide metabolism. The concentrations of nateglinide by co-administration significantly decrease in the presence of gemfibrozil. Therefore close monitoring the pharmacokinetics of nateglinide may be required in the combination therapy of nateglinide with diltiazem, nifedipine or gemfibrozil.

Ⅵ. Acknowledgement

I would like to express my gratitude and appreciation to my advisor,

Dr. Hyo-Kyung Han, for her caring advice, guidance, and help.

I would like to thank Dr. Hye-Sun Gwak, Drs. Jun-Sik Choi and Keon-Wook Kang.

I also like to thank to my lab members, Jung-Hyun Oh, Yo-han Oh, for their great support and help.

I mention them at last, but most grateful to my family and loving one, with all my heart.

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Table 1. Pharmacokinetic parameters of nateglinide (30 mg/kg) following an oral administration in the presence and absence of lipid lowering agents

	Control	**Gemfibrozil**	**Pre-Gemfibrozil**	**Fluvastatin**	**Lovastatin**
C_{max} (μg/ml)	21.7 ± 0.6	10.3 ± 1.5[a]	16.9 ± 2.8	33.4 ± 9.6	25.8 ± 5.4
t_{max} (hr)	0.9 ± 0.1	0.9 ± 0.1	0.5 ± 0.04[a,b]	0.7 ± 0.07	0.8 ± 0.1
$t_{1/2}$ (hr)	4.4 ± 0.8	4.4 ± 1.3	6.5 ± 1.3	5.9 ± 1.2	6.5 ± 1.4
$AUC_{0-\infty}$ (μg · hr/ml)	96.2 ± 14.6	43.1 ± 8.9[a]	70.8 ± 20.4	126.5 ± 23.1	100.2 ± 19.4
AUC_{0-8} (μg · hr/ml)	68.7 ± 7.8	30.8 ± 5.9[b]	42.3 ± 9.1	87.9 ± 20.2	60.9 ± 8.0
CL (L/hr/kg)	0.4 ± 0.08	0.9 ± 0.2[a]	0.7 ± 0.2	0.3 ± 0.04	0.4 ± 0.09
Vz (L/kg)	1.9 ± 0.2	4.5 ± 0.6[a]	5.2 ± 1.2[a]	2.2 ± 0.5	2.9 ± 0.3

[a]Statistically significant compared to Control ($P < 0.05$)

[b]Statistically significant compared to Gemfibrozil ($P < 0.05$)

Pre-Gemfibrozil: Pre-induction by gemfibrozil

Table 2. Pharmacokinetic parameters of nateglinide (30 mg/kg) following an oral administration in the presence and absence of calcium channel blockers

	Control	**Diltiazem**	**Verapamil**	**Nifedipine**	**Pre-Nifedipine**
C_{max} (μg/ml)	21.7 ± 0.6	39.0 ± 7.9[a]	22.2 ± 8.3	39.7 ± 5.3[a]	22.1 ± 2.9
t_{max} (hr)	0.9 ± 0.1	0.8 ± 0.1	0.6 ± 0.05	0.8 ± 0.2	1.0 ± 0.04
$t_{1/2}$ (hr)	4.4 ± 0.8	4.5 ± 0.4	4.8 ± 1.2	7.1 ± 0.5[a]	8.7 ± 2.5[a]
$AUC_{0-\infty}$ (μg · hr/ml)	96.2 ± 14.6	124.6 ± 3.6	82.2 ± 28.4	229.1 ± 33.5[a]	188.1 ± 31.6[a]
AUC_{0-8} (μg · hr/ml)	68.7 ± 7.8	91.8 ± 3.7[a]	55.3 ± 14.8	136.1 ± 20.0[a]	91.7 ± 5.0[a]
CL (L/hr/kg)	0.4 ± 0.08	0.2 ± 0.03	0.5 ± 0.1	0.1 ± 0.02[a]	0.2 ± 0.03
Vz (L/kg)	1.9 ± 0.2	1.9 ± 0.4	2.9 ± 0.6	1.5 ± 0.3	1.8 ± 0.2

[a]Statistically significant compared to Control ($P < 0.05$)

Pre-Nifedipine: Pre-induction by nifedipine

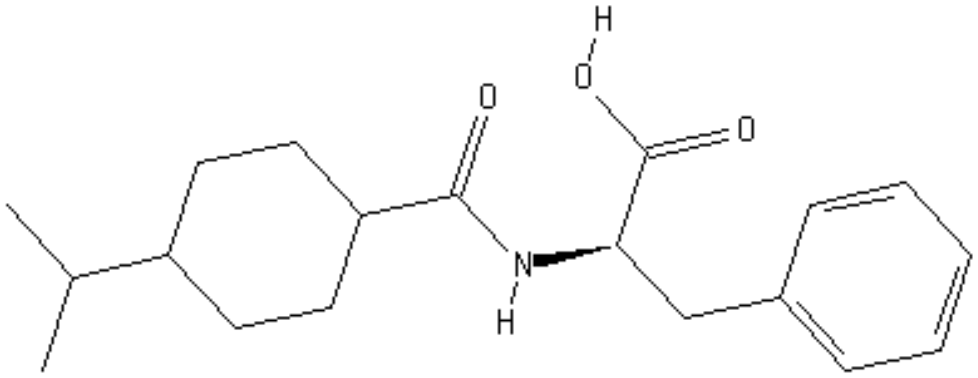

Fig. 1. Chemical structure of Nateglinide (mol. Wt. 317.42)

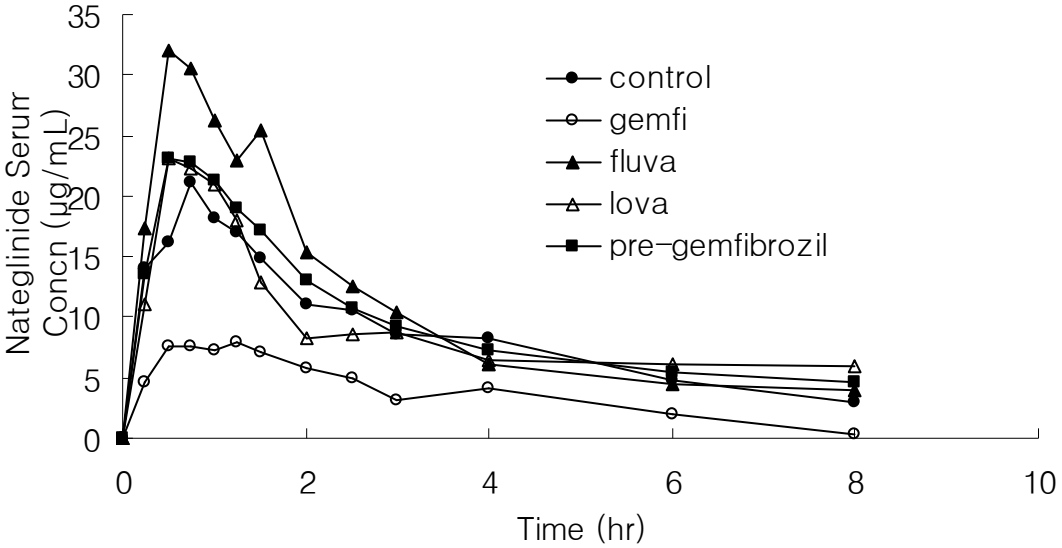

Fig. 2. Serum concentration profiles of nateglinide after an oral administration in the presence and absence of lipid lowering agents

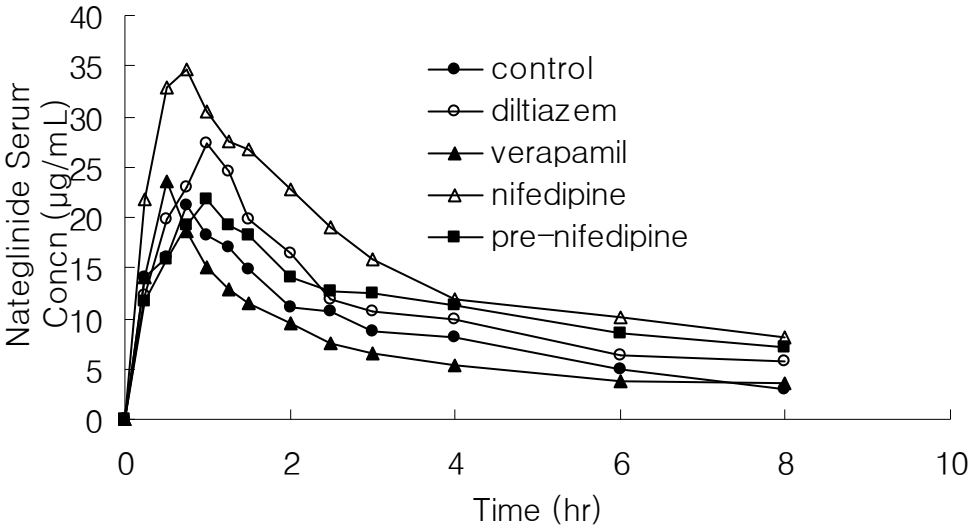

Fig. 3. Serum concentration profiles of nateglinide after an oral administration in the presence and absence of calcium channel blockers