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Effect of Clindamycin on the pharmacokinetics of Nateglinide a *in vivo* evaluations in human volunteers

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ABSTRACT

The intestinal absorption of oral-anti diabetic drugs in type-II Diabetes mellitus is altered when concomitantly administered with other drugs like, antacids, antinuclear drugs, antibiotics and others. A randomized cross over study with two phases and a washout period of 4 weeks was carried out to evaluate the bioavailability of nateglinide with clindamycin. The study has been approved by Institutional ethical committee of Annamalai University. In this study 10 healthy human volunteers received 150mg clindamycin (DALACIN) once daily for 5 days. After and over night fasting on day 6 a single dose of nateglinide 60mg (GLINATE) was given. The blood samples were withdrawn at the following intervals 15, 30, 45, 60, 75, 90, minutes 2, 2.5, 3, 4, 5, 7 hours. The plasma samples (20µl) were injected after separation. The mobile phase comprised of acetonitrile 300ml with 700 ml mixed phosphate buffer (pH 4.0). Analyses were run at a flow rate of 1.0 ml/min with the UV detector operating at a detection wave length of 210 nm, C18 column (25cm × 4.6mm I'd, 5µm) in HPLC and the pharmacokinetic parameters were calculated by using the software Kineticka. (Version 4.4.1, Innaphase, USA). The study reveals that the plasma concentration of nateglinide significantly increased by the concomitant administration of clindamycin.

Keywords: Bioavailability, Antidiabetic drugs, Nateglinide, Clindamycin, Pharmacokinetics, Concomitant administration, Drug interaction.

INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting

from defects in insulin secretion, insulin action, or both.[01] Currently diabetic mellitus is a great threat to the world community with more than 100 million persons suffering from diabetes. The prevalence and incidence of diabetes is increasing in most populations, being more prominent in developing countries as follows, in USA more than 16 million, in republic of China more than 14 million, in Africa more than 20 million. India leads the world largest number diabetic subjects and is being termed the “diabetes capital of the world”. With 50.8 million people currently suffering from diabetes and expected to rise 69.9 million by 2025.[21, 22] Chronic elevation of blood glucose levels leads to many co-existing complications like diabetic retinopathy, diabetic neuropathy, peptic ulcer, diabetic foot ulcer. Drug therapy in Type II diabetes becomes more complex as many individuals are on multiple drug therapy and administer many drugs during the same period of time to treat secondary diabetic complications.[3, 11, 13, and 16] A closer monitoring and supervision of drug therapy is required so that drug related problems can be prevented or detected at an early stage. An increasing number of drug related problems are caused by drug inter actions. [12, 14, 15, 3, 16] Currently clinicians come across the problem of erratic absorption of oral anti diabetic drugs when administered with other drugs prescribed for co-existing diseases. Due to this, bioavailability of oral anti diabetic drugs is altered. Nateglinide is a thiazolidinedione compound used in the treatment type II diabetes. It is an insulin sensitizer that acts as agonist of the preoxsome (PPAR - γ).[5,8] The main active metabolites are M - IV (a hydroxyl derivatives) and M - III (a ketone derivatives); the latter being formed from M -IV (Figure 1).[9] Another metabolite M - II also has pharmacological activity, but its concentrations are low and it does not significantly contribute to the total amount of active species. The circulating concentrations of the metabolites M - IV and M - III are equal to or greater than those of the parent nateglinide and they have considerably longer half-lives than nateglinide.[2] In vitro studies suggested that nateglinide is metabolized by several cytochrome P450 (CYP) enzymes but mainly by CYP2C9 and CYP3A4.[5,8] The lipid lowering fibrate gemfibrozil an inhibitor of CYP2C9 increases AUC of nateglinide when administered with rifampicin. The findings suggested that nateglinide is metabolized mainly by CYP2C9 & CYP3A4 in vivo.[5,8] By taking this consideration clindamycin is inhibitor of CYP3A4 enzyme and hence there may be a chance of alteration in the bioavailability of nateglinide. Our aim is to find out the changes in the bioavailability of nateglinide administered when with clindamycin. The study will ensure that, if it shows no effect on pharmacokinetics of nateglinide, it can be co-administered for treatment of various infections that commonly occur in type II diabetes.

EXPERIMENT SECTION

Materials

The base line HPLC studies carried out using the pure sample of Nateglinide, received as a gift sample from Apex Laboratories, (P) Ltd, Chennai, India. Nateglinide 60 mg as a tablet (GLINATE), Cipla, and Clindamycin 150 mg capsules (CLINCIN), Indi pharma were used in the study. HPLC grade Acetonitrile and Analytical grade Potassium dihydrogen orthophosphate (KH₂PO₄) & orthophosphoric acid, Perchloric acid [7] were used for the study and they were received from Sd fine chemicals, Mumbai. Freshly prepared double distilled, deionized water, filtered through 0.2 μ m nylon filter (47 mm) using Millipore unit (USA), was used throughout the experiments[19] The drug analysis was carried out using HPLC system (UFLC Shimadzu Prominence LC -20 AD) having isocratic pump (LC 20 AD UP) Rheodyne injector port, and SPD M20A Shimadzu prominence diode array detector. The data interpretation was done with inbuilt Shimadzu system controller (SCL - 20 AVP).

Subjects

Ten men diabetic patients, age ranged from 21-30 yrs and weight ranged from 57-79 kg were participated in the study after obtaining a written informed consent. The patients were ascertained to be healthy by medical history, clinical examination and routine laboratory tests. None even on medication. The study was carried out at Rajah Muthiah Medical College and Hospital, Annamalai University and it was approved by the institutional human ethics committee of Annamalai University.

Study design

A randomized cross over study with two phases and a washout period of 4weeks was carried out. Volunteers took 150mg clindamycin (CLICIN) 150 mg orally once daily at 20.00 h (8 am) for 5 days. After an overnight fast on day 6 a single dose of nateglinide (GLINATE) 60mg was administered orally with 150ml of water.^[2] Volunteers received a standard meal 3h after dosing. Volunteers received light standard meals 7th h and 11th h after dosing.

Pharmacokinetics of Nateglinide ^[24]

Blood samples (5ml) were drawn after administered of pioglitazone by orally at 0.5, 1, 2, 3, 4, 5, 7, 9, 12 later through median capital vein, and collected in EDTA treated vacutainers tubes. Blood samples were immediately centrifuged at 5000 rpm for 10 min to obtain plasma and stored at -20°C until analysis. Nateglinide concentration was determined by addition of 100µl acetonitrile with 100µl of plasma to deproteinise the proteins. The mixture was vortex mixed for 5 min after which it was centrifuged at 10000 rpm for 10 min. 100µl of supernatant liquid was injected into the HPLC system for analysis [5.9]. The UV detector was set at 210 nm for the present analysis. C18 column (4.6 mm × 250 mm, 100 Å) Luna. PHENOMINEX, USA was set at 30°C. The mobile phase comprised of Methanol: acetonitrile: mixed phosphate buffer (pH4.0) at a ratio of (70:10:20) at a flow rate of 1.2 ml.min⁻¹.^[3]

Pharmacokinetic analysis

Peak plasma concentration (C_{max}), Time to C_{max} (t_{max}), AUC from 0 to 12h (AUC_{0-12}), $t_{1/2}$. All the pharmacokinetic and statistical data were calculated by using the software *Kinetic*, (Version 4.4.1, Innaphase, USA).

RESULTS AND DISCUSSION

Currently the management of type II diabetes becoming more complex since the recommended global approach of combination drug therapy has increased the risk of pharmacokinetics interactions in patients with diabetes.^[18] The activity of one drug could alter the pharmacokinetics of another drug and it may be due to risk of the enzyme inverse reaction upon the plasma levels of concomitantly administered drugs.^[7] Nateglinide is rapidly absorbed in GIT, its oral bioavailability exceeds 80%, and it is extensively metabolized by hydroxylation and oxidation to form active and inactive metabolites in the live. *In vivo* studies suggest that the drug is metabolized by several cytochrome P450 (CYP) enzymes, but mainly by CYP2C9 and CYP3A4^[23]. Clindamycin is an antibiotic used to treat secondary diabetic infections. *In vitro* studies suggested clindamycin is a moderate inhibitor of CYP3A4.^[7]

It is clinically important to find out the interaction between clindamycin and co-administered drugs, which are metabolized by the enzyme CYP3A4. The present study was designed to clarify the effect of clindamycin on the pharmacokinetics of nateglinide through CYP3A4 enzyme inhibition. By considering into the account of above reasons. The effect of clindamycin on the pharmacokinetics of nateglinide was assessed using a randomized, two cross over study with wash

out period of 4 weeks. Volunteers took 150mg of clindamycin (CLINCIN) orally once daily at 20.00 hrs (8pm) for 5 days. After an overnight fasting on 6 day at 9.00 am single dose of 60mg nateglinide (GLINATE) was administered orally with 150ml of water. The blood samples were drawn before and after administration of nateglinide. The separated plasma was analyzed in HPLC system. The result showed that the C_{max} was 4736 mg in Nateglinide alone in the time of 1 hrs but the C_{max} reached 4916 mg in the time of 2 hrs when administered with clindamycin there is no alteration in absorption of drug. The T_{1/2} of Nateglinide alone was 1.57 and T_{1/2} of clindamycin was 2.3, it had occurred because of inhibition of CYP3A4 by clindamycin. The data obtained from the analysis shows that of clindamycin increases the C_{max}, AUC and t_{1/2} of nateglinide after 2hrs (Figure 1 & 2). It is observed that clindamycin affects the pharmacokinetics of nateglinide by moderate inhibition of CYP3A4. Hence the metabolism of nateglinide purely depends on activity of CYP2C9 enzyme only and extends the time period of metabolism of nateglinide and remains in the systemic circulation for longer period as a result the nateglinide showed longer hypoglycemic action. It may lead to the increasement of other complications like adverse reaction and toxicity of nateglinide.

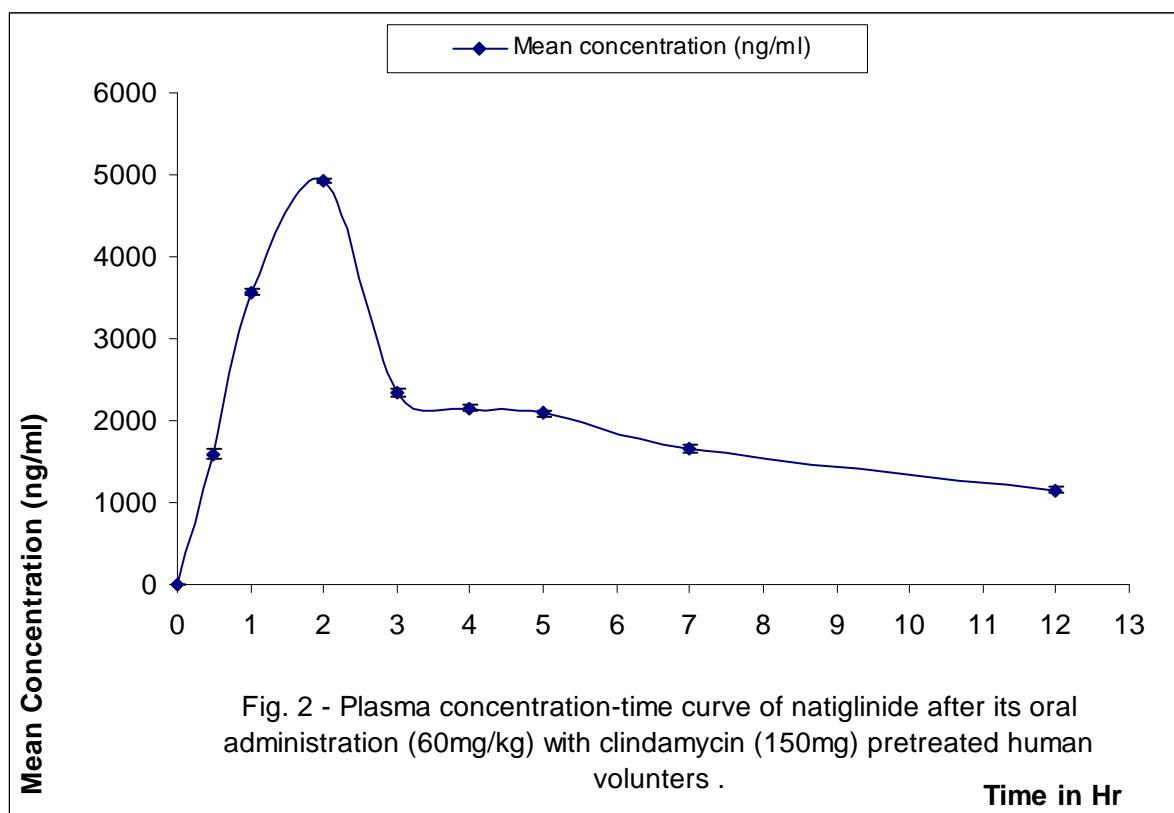
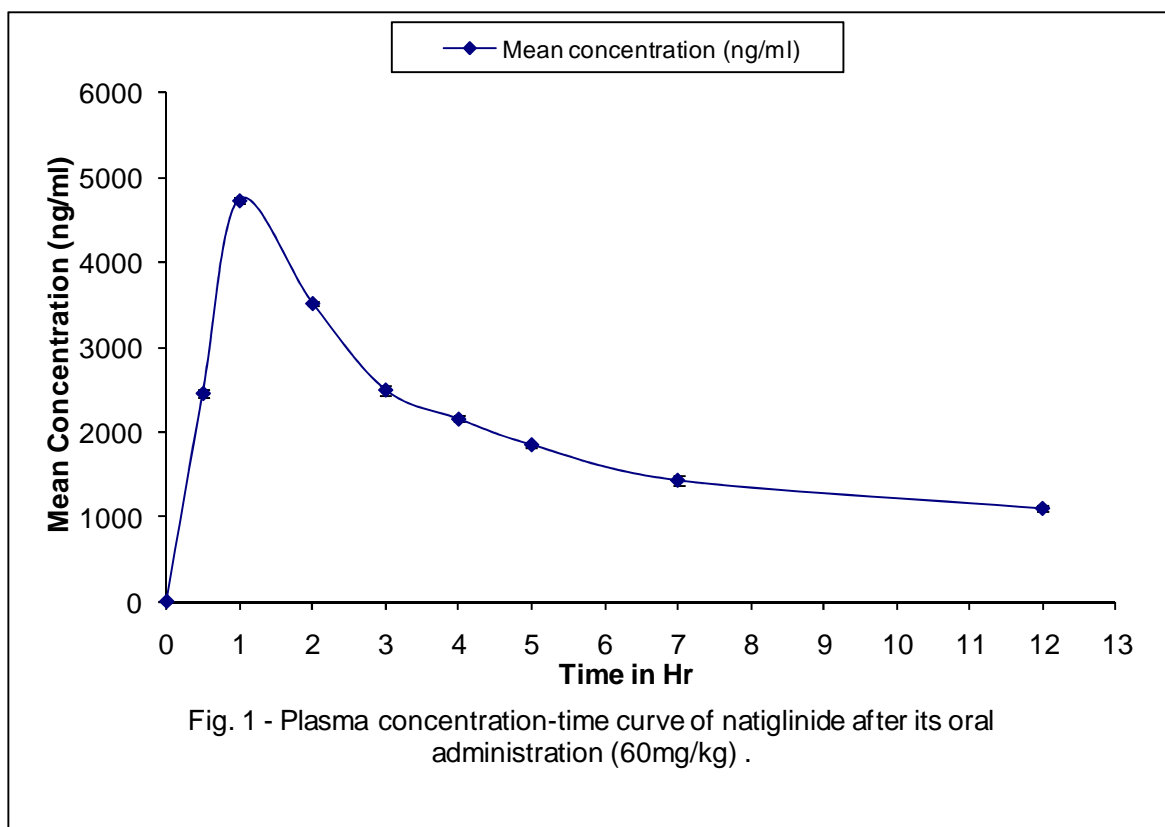
CONCLUSION

The present study was carried out with an attempt to investigate any possible interaction occurs between clindamycin and nateglinide in the treatment of TypeII diabetes with secondary diabetic infections. The drug concentration was compared to standard chromatograms. Clindamycin was found to increase the concentration of nateglinide from 2 hr onwards as compared to standard phase (nateglinide alone), decreases elimination rate (t_{1/2}) of nateglinide in plasma (Table 1) and also revealed that C_{max} of nateglinide was not affected much. It clarifies that there is no change in the intestinal microsomal activity but changes the hepatic microsomal activity by CYP3A4 mediated inhibition.

Table-1 Pharmacokinetic parameters of nateglinide in clindamycin pretreated human volunteers

Parameter	Nateglinide alone	Clindamycin phase
C _{max} (ng/ml)	4736 ± 34.4	4916 ± 34.53
T _{max} (hrs)	01 ± 0	01 ± 0
AUC(ng.h/mL)	21450 ± 0.36	24035 ± 0.85
T _{1/2} (hr)	1.57 ± 0.34	2.33 ± 0.55
RB(%)	100 ± 0.0	112.5 ± 14

Volunteers took 150mg clindamycin (CLICIN 150mg) orally once daily for 5 days. After an overnight fast on the day 6 a single dose of 60mg nateglinide (GLINATE 60mg) was administered orally there after pharmacokinetics of nateglinide was carried out. T_{max} - time to reach; C_{max} - peak plasma concentration; AUC - area under the plasma concentration curve; T_{1/2} - half life; RB - relative bioavailability.



This finding indicates that clindamycin inhibit the metabolism of nateglinide during elimination phase. Some inter individual variation in the extent of the interaction was evident with increase of AUC of nateglinide from 0 –12 h as compared to standard phase (nateglinide alone). Thus the time

interval between administration of clindamycin and nateglinide affects the magnitude of interaction. The increase in plasma concentration of nateglinide was found to be higher when it is co administered with clindamycin and it may increase the blood glucose lowering efficacy of nateglinide. This may lead to accumulation of drug in the body, which may lead to toxicity. Therefore, it is advisable to monitor blood glucose level when starting the therapy with clindamycin to adjust the required dosage of nateglinide.

In conclusion, the present study suggests that clindamycin acts as inhibitor of CYP3A4. Coadministration of clindamycin with nateglinide causes substantial increase in plasma concentration of nateglinide by the inhibition of CYP3A4 and it may lead the risk of toxicity in diabetic patients.

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