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Effect of Pantoprazole in the Pharmacokinetics of Metformin Hydrochloride in the Management of Type – II Diabetes – A Human Study

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ABSTRACT

The intestinal absorption of oral-anti diabetic drugs in the treatment of type-II diabetes is altered when concomitantly administered with antacids, antinuclear agents, antibiotics and others. A randomized cross over study in two phases with a washout period of 4 weeks was carried out to evaluate the bioavailability of "metformin hydrochloride" administered with pantoprazole. In the present study 10 diabetic patients received pantoprazole tablet at a dose of 20mg once daily for 5 days. After overnight fasting, on 6th day a single dose of 500 mg metformin hydrochloride tablet was given. The blood samples were withdrawn at various time intervals upto 12 hours. The 100µl of deproteinised supernatant liquid was injected into HPLC. 0.01M potassium dihydrogen orthophosphate (pH 3.5) and acetonitrile at a ratio of 60:40 v/v was used as a mobile phase. Analyses were run by using Luna cyano column at a flow rate of 1.0 ml.min^{-1} using diode array detector operating with a detection wave length of 234 nm. All the pharmacokinetic parameters were calculated by using software *Kinetica.* The results of study revealed that there was no significant change in the pharmacokinetics of metformin hydrochloride when it was concomitantly administered with pantoprazole.

Keywords: Bioavailability, metformin hydrochloride, pantoprazole, pharmacokinetics, concomitant administration, drug interaction.

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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 (WHO/NCD/NCS/99.2) [1]. 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 countries like USA (< 16 million), Republic of China (< 14 million) and in Africa (< 20 million). India leads the world largest number of diabetic subjects and is being termed as "diabetes capital of the world", with 40.9 million people currently suffering from diabetes and expected to rise 69.9 million by 2025 [2]. Chronic elevation of blood glucose levels after onset of diabetes leads to many co-existing complications like diabetic retinopathy, diabetic neuropathy, peptic ulcer, diabetic foot ulcer and others. 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]. Nagger and co-workers carried out a *in vitro* evaluation of antidiabetic drugs metformin hydrochloride, glibenclamide, acetohexamide, tolbutamide, carbutamide, tolazamide, and glymidine with various antacids and adsorbents such as magnesium trisilicate, aluminum hydroxide, calcium carbonate, magnesium oxide, talc, kaolin as well as charcoal and the authors reported that the antidiabetic drugs are strongly interacting with antacids/adsorbents in various degrees. The author's recommended to confirm such drug interactions in *in vivo* [4]. In addition to these, an increasing number of drugs related complications arise day to day due to drug interactions [5-9]. Hence, a closer monitoring and supervision of multiple drug therapy is required for diabetes so as to avoid drug related complications. Concomitant administration of antidiabetic drugs with other drugs alters the pharmacokinetics of anti diabetic drugs due to erratic absorption. Recently, the clinician and clinical pharmacologist focusing their attention to address these complications for the better management of type II diabetes mellitus. The aim of the present study was to evaluate the bioavailability of Metformin hydrochloride when it concomitantly administered with proton pump inhibitor pantoprazole hydrochloride, since metformin hydrochloride is a biguanide, used in the treatment of type II diabetes [10]. *In vitro* studies revealed that Metformin hydrochloride is metabolized by several cytochrome (CYP) P450 enzymes but mainly by CYP2C11.2D1 and 3A1/2 [11]. This study was carried in line with our previous unpublished report, showed a significant alteration in the bioavailability of antidiabetic drug "Pioglitazone" when it concomitantly administered with an antibiotic "Clindamycin".

MATERIALS AND METHODS

Materials

The base line HPLC studies carried out using the pure sample of Metformin hydrochloride, received as a gift sample from Apex Laboratories, (P) Ltd, Chennai, India. The Metformin hydrochloride as a 500 mg tablets (GLICIPHAGE), Franco-Indian, Chennai and Pantoprazole as a 20 mg tablets (PANTOCID), Misha Biotech were used in the study. HPLC grade Acetonitrile and Analytical grade Acetic acid, Perchloric acid [13,14] were used for the study and they were received from Sd fine chemicals, Mumbai. Freshly prepared double distilled, deionized water, filtered through 0.2µm nylon filter (47 mm) using Millipore unit

(USA), was used throughout the experiments [15]. 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 and that informed consent was obtained.

Study design

A randomized cross over study with two phases and a washout period of 4 weeks was carried out. Volunteers took 20 mg of Pantoprazole orally as a tablet, once daily at 8 am consecutively for 5 days. After an overnight fast, on 6^{th} day single dose of Metformin hydrochloride [12] as a 500 mg tablet was administered orally with 150 ml of water. Volunteers received a standard meal at 3^{rd} hr after dosing and additional light standard meals at 7^{th} hr and 11^{th} hr [15].

EXPERIMENTAL

Pharmacokinetic evaluation of metformin hydrochloride

The pharmacokinetic evaluation of metformin hydrochloride was carried out as per the method described by Yuen and co-workers [13] using HPLC system (UFLC Shimadzu Prominence LC -20 AD) consisted of 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). 5 ml of blood samples were withdrawn after oral administration of metformin hydrochloride as a 500 mg tablet. The blood samples were withdrawn at various time intervals such as 1, 2, 3, 4, 5, 7, 9 and 12 hrs and transferred into EDTA treated vacationer tubes and centrifuged at 5000 rpm for 10 min, the plasma separated and stored at 20°C until the analysis. The deproteinisation of the plasma was carried out by the treatment with perchloric acid at a ratio of 1:1, mixed thoroughly by vortex for 5 min and followed by centrification at 10,000 rpm for 10 min. The concentration of metformin hydrochloride was estimated by injecting 100 µl of deproteinised supernatant liquid into HPLC using the mobile phase comprised of 0.01M potassium dihydrogen orthophosphate (pH 3.5) and acetonitrile at a ratio of 60:40 v/v, respectively.

Pharmacokinetic analysis

The drug concentrations of metformin hydrochloride and pantoprazole were determined with the comparison of standard chromatograms. All the pharmacokinetic and

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statistical analysis were carried out by the interpretation of our data using the software *Kinetica* (Version 4.4.1, Innaphase, USA) [15] and the following parameters such as Peak plasma concentration (C_{max}), Time to C_{max} (T_{max}), AUC from 0 to 12h (AUC_{0-12}), $t_{½}$ were calculated.

RESULTS AND DISCUSSION

In vitro studies suggested that the Metformin hydrochloride metabolized by several cytochrome (CYP) P450 enzymes, mainly by CYP2C11.2D1 and 3A1/2 [11]. Pantoprazole is a proton pump inhibitor and its metabolized by polymorphically expressed CYP2C19 and by CYP3A4. A randomized, two cross over study with a wash out period of 4 weeks was carried out. Volunteers administered 20 mg of Pantoprazole orally as a tablet, once daily at 8 am consecutively for 5 days. After an overnight fast, on 6th day single dose of Metformin hydrochloride as a 500 mg tablet was administered orally with 150 ml of water. Volunteers received a standard meal at 3rd hr after dosing and additional light standard meals at 7th hr and 11th hr. Blood samples were withdrawn before and after administration of Metformin hydrochloride. The plasma was separated and analyzed in HPLC system. The pharmacokinetic parameters observed with administration of metformin hydrochloride alone such as the area under curve (AUC_{0-t}), ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), the time taken to reach the maximum concentration (T_{max}), rate of elimination (K_{el}) and plasma half life of drug ($t_{½}$) and the corresponding values are 4791±10.38, 4810±10.27, 1540±45.11, 2.20±0.58, 0.22±0.03 and 2.50±0.39 respectively. The effect of pantoprazole on the pharmacokinetic of metformin hydrochloride was also measured by concomitant administration with pantoprazole. The results of the study such as the area under curve (AUC_{0-t}), ($AUC0_{-\infty}$), maximum plasma concentration (C_{max}), the time taken to reach the maximum concentration (T_{max}), rate of elimination (K_{el}) and plasma half life of drug ($t_{½}$) and the corresponding values are 4477±9.87, 4547±10.32, 1565±38.23, 2.25±0.16, 0.20±0.03 and 2.55±0.51 respectively (Table 1) . The results of the study revealed that the pantoprazole does not alter the AUC, C_{max} and $t_{1/2}$ of metformin hydrochloride (Figure 1&2). The study revealed that there was no alteration of pharmacokinetic parameters of metformin hydrochloride when co administered with pantoprazole. The results are unlike our previous study of pioglitazone [17,18] with clindamycin in diabetic patients, showed marked increase in the bioavailability when they co administered. The results revealed that the bioavailability of pioglitazone was increased when administered with clindamycin (our unpublished data).

CONCLUSION

The present study evaluated the effect of pantoprazole on the Pharmacokinetics of metformin hydrochloride and to investigate any possible interaction occurs between pantoprazole and metformin hydrochloride. The drug concentrations of metformin hydrochloride and pantoprazole were determined in comparison with standard HPLC chromatograms.

From the results it was found that the pantoprazole does not change the plasma concentration of metformin hydrochloride. In addition to these the concomitant use of pantoprazole does not change the glycemic effect of metformin hydrochloride and no drug

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interaction has been observed. Hence, these drugs can be administered together for the better management of Type 2 diabetes and associated secondary disorder “ulcer”.

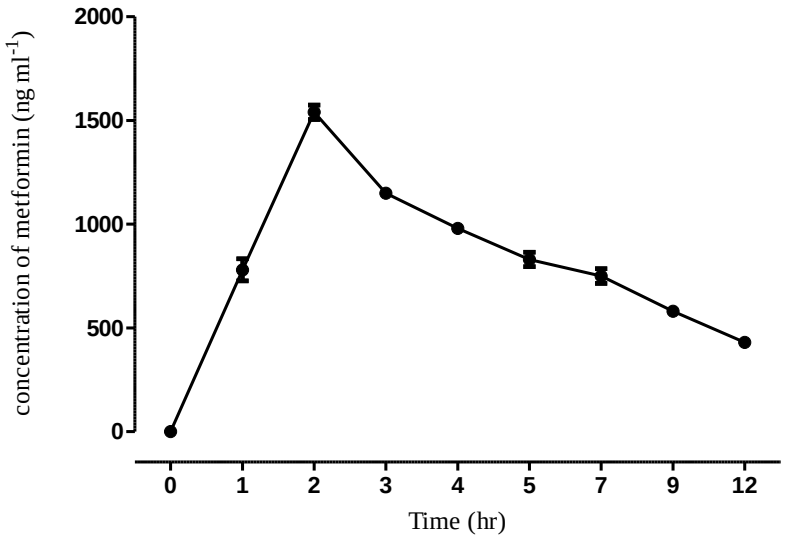
Table. 1 Pharmacokinetic parameters of metformin hydrochloride in Pantoprazole pretreated human volunteers

Pharmacokinetics parameter	Metformin hydrochloride alone	Metformin hydrochloride with Pantoprazole
AUC_{0-t} (ng *h/mL)	4791 ± 10.38	4477 ± 9.87
$AUC_{0-\infty}$ (ng*h/mL)	4810 ± 10.27	4547 ± 10.32
C_{max} (ng/mL)	1540 ± 45.11	1565 ± 38.23
T_{max} (h)	2.20 ± 0.58	2.25 ± 0.16
K_{el} (ng/mL)	0.22 ± 0.03	0.20 ± 0.03
$t_{1/2}$ (h)	2.50 ± 0.39	2.55 ± 0.51

Volunteers took 500mg Metformin hydrochloride (GLYCIPHAGE) orally once daily for 5 days. After an overnight fast on the day 6 a single dose of 20mg Pantoprazole (PANTOCIT) was administered orally there after pharmacokinetics of pioglitazone 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.

Figure 1:

Plasma time concentration of metformin alone



Plasma Concentration time curve of Metformin hydrochloride after its oral administration (500mg) in human volunteers. The experiments were carried out by using by the plasma samples of diabetic patients. Each point represents the mean ± standard deviation (n=10)

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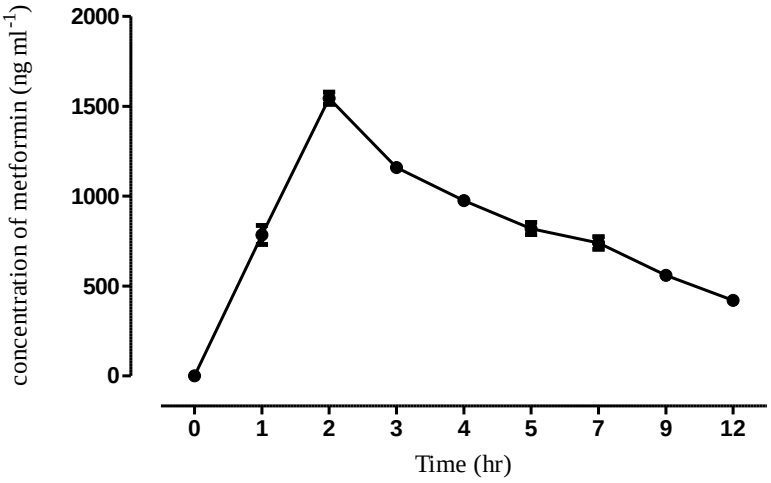
Figure 2

Plasma time concentration of metformin
concomitanly administred with pantoprazole



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Plasma Concentration – time curve of Metformin hydrochloride after its oral administration (500mg) with Pantoparazole (20mg) in pre-treated human volunteers. The experiments were carried out by using by the plasma samples of diabetic patients. Each point represents the mean ± standard deviation (n=10)

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