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Pharmacokinetic Interactions of Glipizide with Esomeprazole in Normal, Diabetic and Ulcerative Rats

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Abstract

The present study was carried out to evaluate the drug-drug interactions between esomeprazole and glipizide. Interaction of esomeprazole (Eso), the known antiulcer drug with antidiabetic agent, glipizide (Gli) was evaluated in healthy, diabetic and ulcerative rats. Single day (SD) and multiple day (MD) pharmacokinetic studies were performed for glipizide and esomeprazole in normal, diabetic and ulcerative animals. Blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 8 and 24 hours (hr) and pharmacokinetic parameters were determined. Both single and multiple days treatment of glipizide has shown no effect on pharmacokinetic profile of esomeprazole, while esomeprazole influenced the pharmacokinetic properties of glipizide in both normal and diabetic rats. This may be due to inhibition of CYP (cytochrome P-450) enzyme by esomeprazole, the enzyme through which glipizide gets metabolized. The findings of the present study suggested that there is potential pharmacokinetic interaction between glipizide and esomeprazole in rats.

Key words: *Glipizide, Esomeprazole, Streptozotacin, Pharmacokinetic.*

Introduction

In many chronic ailments, the multi drug therapy may be advocated to mitigate the severity of or to avoid the development of possible resistance. There is every possibility of occurrence of drug-drug interactions when multiple drugs were administered simultaneously. These interactions may be so severe to cause mortality or may nullify the therapeutic efficacy of the treatment. Drug interactions have become a significant issue in health care system. These drug interactions can be explained by alteration in the pharmacokinetic parameters including inhibition or induction of metabolic enzymes or by alterations in pharmacodynamic properties of one or both of the drugs. Many of the major pharmacokinetic interactions occur due to induction or inhibition of hepatic cytochrome P450 enzymes[1,2]. There are certain patients who may be suffering with more than one disease at a time, which may require chronic treatment such as diabetes and gastric ulcer. As both diseases require chronic treatment or chronically used as prophylaxis. In any case, it can create a scenario where one has to use multiple drug therapy for such diseases. This will lead to drug-drug interactions, where one drug may influence the pharmacokinetic or pharmacodynamic profile of the other[3].

Diabetes is 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. There are reports that several patients suffering from diabetes are prone to peptic ulcer infections[4]. Antiulcer drugs such as ranitidine, famotidine, omeprazole and

lansoprazole potentiates the action of many sulfonylureases, when they are used concomitantly for a prolong period of time[5,6,7]. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus[8] and it is extensively metabolized in the liver by CYP2C9[9] and CYP3A4[10,11,12]. Esomeprazole is a Proton pump inhibitor and S-isomer of omeprazole. Esomeprazole is extensively metabolized by CYP3A4 and CYP2C19 in liver[13].

On perusal of literature survey, we found that the interaction of glipizide and esomeprazole has not been elucidated. Therefore, the present study was conducted to assess the interaction between esomeprazole and glipizide in normal, diabetic and ulcerative rats.

Materials and Methods

Drugs: Esomeprazole was purchased from Sigma–Aldrich Co, St Louis, MO, USA and glipizide was obtained as gift samples from Matrix Pvt. Ltd, Hyderabad. All other chemicals used were of analytical grade.

Experimental animals: Wistar rats weighing 200 to 250 g were used for the present study. Animals were housed under a standard 12 hr: 12hr light/dark cycle and were provided with food and water *ad libitium*. Animals were acclimated to laboratory conditions before testing. The animal protocol was approved by the Institutional Animal Ethical Committee of Kalol institute of pharmacy, India.

Experimental procedures:

Streptozotacin (STZ) induced diabetes[14]: At neonatal stage, STZ was administered at day 2 and day 3 of birth at a dose of 45 mg/kg in citrate buffer at pH 4.5, which result in diabetic condition. At the end of 8th week of their age, oral glucose tolerance test was done at a dose of 3 g/kg of glucose to evaluate the diabetic condition in rats. The rats which have 45% high glucose AUC compared to normal control were selected for the study.

Indomethacin induced chronic gastric ulcer[15]: The rats were treated with indomethacin orally at a dose of 1 mg/kg per day for a period of 12 weeks. At the end of 12 weeks, animals were selected for the study.

Pharmacokinetic interaction study in normal, diabetic and ulcerative rats:

Wistar rats were randomly distributed into different groups of six animals in each group. They were housed in well ventilated polypropylene cages and maintained on uniform diet and temperature with 12 hr light and dark cycle. Glipizide was administered at a dose of 50 mcg/kg and esomeprazole at a dose of 30 mg/kg, orally to their respective groups. These animals were mainly divided into two sub groups as follows: Normal and diseased animals. In normal rats, Group 1 was vehicle control, which received vehicle. Group 2 and 3 were served as treatment groups, which received esomeprazole and glipizide respectively. Group 4 was served as treatment group (SD), which received esomeprazole, followed by glipizide after 30 minutes. Group 5 was served as treatment group (SD), which received glipizide, followed by esomeprazole after 30 minutes. Group 6 was served as treatment group (MD), which received esomeprazole for 8 days, followed by glipizide after 30 minutes on 8th day. Group 7 was served as treatment group (MD), which received glipizide for 8 days, followed by esomeprazole after 30 minutes on 8th day.

In disease rats, Group 1 and 2 were served as diabetic and ulcerative control, which received vehicle. Group 3 rats were diabetic which received glipizide and group 4 rats were ulcerative which received esomeprazole. Group 5 rats were diabetic (SD), which received esomeprazole, followed by glipizide after 30 minutes. Group 6 rats were ulcerative (SD), which received glipizide, followed by esomeprazole after 30 minutes. Group 7 rats were diabetic (MD), which received esomeprazole for 8 days, followed by glipizide after 30 minutes on 8th day. Group 8 rats were ulcerative (MD), which received glipizide for 8 days, followed by esomeprazole after 30 minutes on 8th day.

All the animals were over night (12 hours) fasted with water *ad libitum.* Animals were administered with their respective treatments. Blood was collected at 0, 0.25, 0.5, 1, 2, 4, 8 and 24th hour. Samples were centrifuged at 8000 rpm

for 10 minutes, plasma was collected and subjected for high performance liquid chromatography (HPLC) analysis.

Pharmacokinetic data analysis[16]: The maximum plasma concentration (C_{max}), time needed to reach the maximum plasma concentration (T_{max}), area under the concentration– time curve ($AUC_{0–24}$), mean residence time (MRT), elimination rate constant (K_{el}) and half life ($T_{1/2}$) were calculated using non compartmental pharmacokinetic model of WinNonlin-5.3.

Statistical analysis: All the means are presented with their standard error mean (mean ±SEM). The pharmacokinetic parameters were compared using one-way ANOVA, followed by Dunnett test.

Results

The mean plasma levels were evaluated for glipizide and esomeprazole alone and their combinations in both normal and diseased condition. In single dose study, Glipizide alone has shown significant increase in C_{max} in both normal and diabetic condition (table-1 and 2). Single day treatment with esomeprazole potentiate the pharmacokinetic profile of glipizide in both normal, (AUC, 77.44±4.13 vs. 58.12±2.51, P<0.05), (C_{max}, 8.54±0.27 vs. 6.73±0.45, P<0.01), ($T_{1/2}$, 4.34±0.16 vs. 3.23±0.24, P<0.01) and diabetic (AUC, 83.77±5.82 vs. 65.00±4.77, P<0.05), (C_{max}, 9.18±0.43 vs. 7.35±0.33, P<0.01), ($T_{1/2}$, 4.11±0.09 vs. 3.37±0.13, P<0.001) rats. While glipizide has not shown any significant improvement in pharmacokinetic properties of esomeprazole.

In multiple days treatment, esomeprazole shown significant increase in the pharmacokinetic parameters of glipizide in both normal (AUC, 106.42±6.15 vs. 58.12±2.51, P<0.001), (C_{max}, 11.92±0.22 vs. 6.73±0.45, P<0.001), ($T_{1/2}$, 4.71±0.10 vs. 3.23±0.24, P<0.001) and diabetic (AUC, 104.91±6.73 vs. 65.00±4.77, P<0.01), (C_{max}, 12.05±0.30 vs. 7.35±0.33, P<0.001), ($T_{1/2}$, 4.98±0.06 vs. 3.37±0.13, P<0.001) rats. While glipizide has not shown any significant improvement in pharmacokinetic properties of esomeprazole

Tables

Table 1: Mean pharmacokinetic parameters of glipizide alone and during esomeprazole treatment in normal rats

Parameters	Glipizide	Glipizide+Esomeprazole (SD)	Glipizide+Esomeprazole (MD)
C_{max} (mcg/ml)	6.73±0.45	8.54±0.27**	11.92±0.22***
T_{max} (hr)	4.00±0.00	4.00±0.00	4.00±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	58.12±2.51	77.44±4.13*	106.42±6.15***
$T_{1/2}$ (hr)	3.23±0.24	4.34±0.16**	4.71±0.10***
K_{el} (1/hr)	0.219±0.02	0.160±0.01*	0.147±0.01**
MRT (hr)	5.76±0.01	5.96±0.05	5.92±0.09

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to glipizide control**.**

Table 2: Mean pharmacokinetic parameters of glipizide alone and during esomeprazole treatment in diabetic rats

Parameters	Glipizide	Glipizide+Esomeprazole (SD)	Glipizide+Esomeprazole (MD)
C_{max} (mcg/ml)	7.35±0.33	9.18±0.43**	12.05±0.30***
T_{max} (hr)	4.00±0.00	4.00±0.00	4.00±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	65.00±4.77	83.77±5.82*	104.91±6.73**
$T_{1/2}$ (hr)	3.37±0.13	4.11±0.09***	4.98±0.06***
K_{el} (1/hr)	0.207±0.012	0.169±0.001**	0.139±0.002***
MRT (hr)	5.80±0.25	6.00±0.07	5.95±0.10

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to glipizide control.

Table 3: Mean pharmacokinetic parameters of esomeprazole alone and during glipizide treatment in normal rats

Parameters	Esomeprazole	Esomeprazole+Glipizide (SD)	Esomeprazole+Glipizide (MD)
C_{max} (mcg/ml)	1.22±0.04	1.36±0.03	1.23±0.05
T_{max} (hr)	1.00±0.00	1.00±0.00	1.00±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	11.25±0.92	11.91±1.52	10.12±0.79
$T_{1/2}$ (hr)	3.51±0.23	3.63±0.27	3.45±0.18
K_{el} (1/hr)	0.199±0.01	0.193±0.01	0.202±0.01
MRT (hr)	5.39±0.16	5.34±0.29	5.16±0.15

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to esomeprazole control.

Table 4: Mean pharmacokinetic parameters of esomeprazole alone and during glipizide treatment in ulcerative rats

Parameters	Esomeprazole	Esomeprazole+Glipizide (SD)	Esomeprazole+Glipizide (MD)
C_{max} (mcg/ml)	1.53±0.06	1.58±0.05	1.63±0.06
T_{max} (hr)	1.00±0.00	1.33±0.33	1.00±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	13.49±1.20	13.17±1.04	13.97±1.18
$T_{1/2}$ (hr)	3.57±0.25	3.56±0.15	3.66±0.22
K_{el} (1/hr)	0.196±0.01	0.195±0.01	0.191±0.01
MRT (hr)	5.32±0.12	5.34±0.22	5.42±0.18

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to esomeprazole control.

Figures

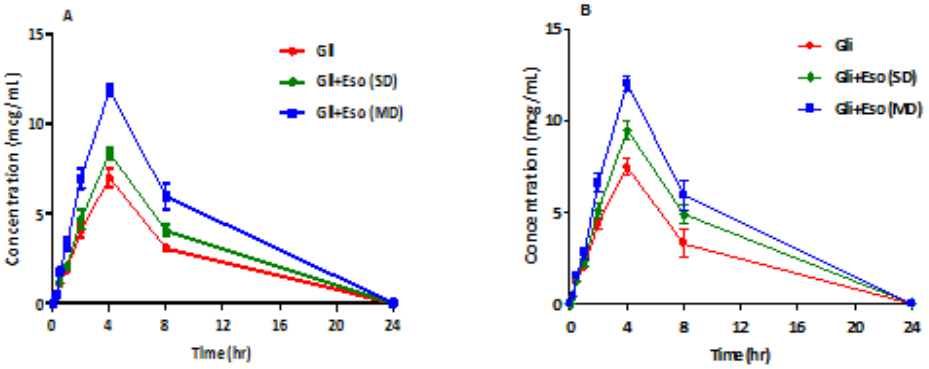
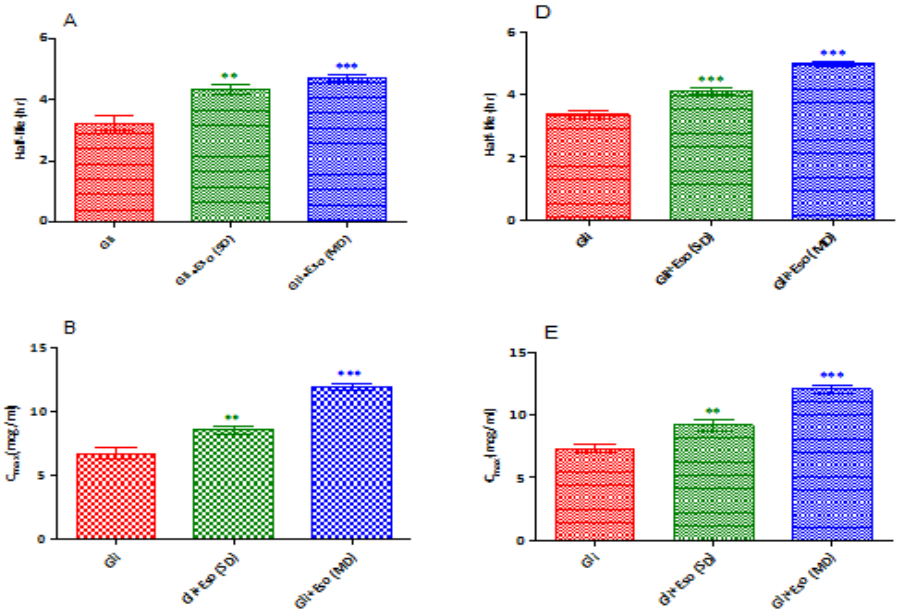


Fig.1. Plasma concentrations time curves of (Gli) glipizide following its oral administration at 50 mcg/kg in control and (Eso) esomeprazole (30 mg/kg) pre-treated (SD & MD) normal (A) and diabetic (B) rats. Data are expressed as mean±SEM in (n = 6) rats.



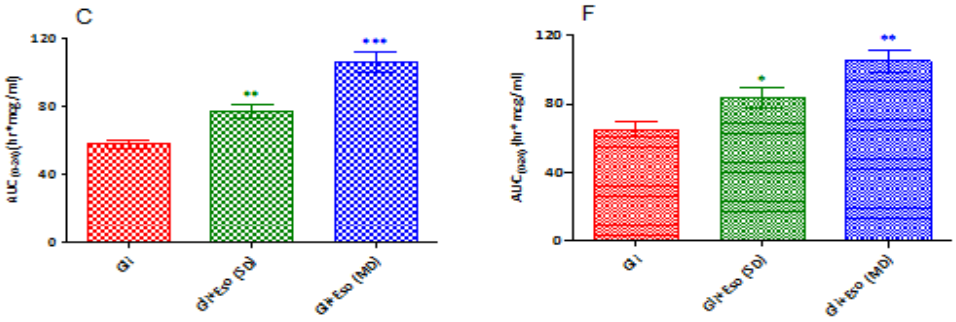


Fig.2. A, B, C and D, E, F represent pharmacokinetic parameters in normal and diabetic rats respectively. Half life, C_{max} and AUC of glipizide following its oral administration at 50 mcg/kg in control and esomeprazole (30 mg/kg) pre-treated (SD & MD) normal (A,B,C) and diabetic (D,E,F) rats respectively. Data are expressed as mean±SEM in (n = 6) rats.

Discussion

Chronic elevation of blood glucose levels leads to many co-existing complications like diabetic retinopathy, diabetic neuropathy, delay in healing of gastric 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[17]. 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 interactions[17]. Currently, the management of type II diabetes becoming more complex since the recommended global approach of combination drug therapy has increased the risk of pharmacokinetic 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[19].

Esomeprazole, the (S)-isomer of omeprazole, is the first proton pump inhibitor developed as a single isomer for the treatment of acid-peptic diseases. Esomeprazole is extensively metabolized by CYP3A4 and CYP2C19 isoenzyme in the liver[13]. Glipizide is highly potent second generation sulfonylurea derivative which is used for the treatment of type II diabetes mellitus. Glipizide is extensively metabolized in the liver by CYP2C9[9] and CYP3A4[10,11,12]. Alteration in pharmacokinetic profile of esomeprazole and glipizide was assessed by interaction between these drugs in both normal and diseased rats. Single dose study showed that glipizide administration did not potentiate the pharmacokinetic parameters of esomeprazole. Glipizide has not shown any significant improvement in absorption, metabolism and excretion of esomeprazole in both healthy and diseased rats, which indicates no significant interaction occurred. While, single dose administration of esomeprazole stimulated the pharmacokinetic profile of glipizide in both healthy and diabetic rats which indicates an inhibition of glipizide metabolism leading to increased AUC and high plasma levels of glipizide in both normal and diabetic rats. This confirmed interaction occurred at absorption site. Prior administration of esomeprazole further increases the half life and decreases the K_{el} when compared with glipizide alone which indicates interaction occurred at metabolism and excretion site also. In multiple dose study, repeated dosing of glipizide did not influence the pharmacokinetic profile of esomeprazole in both healthy and ulcerative rats. Hence, interaction at absorption, metabolism and excretion site has been ruled out. While, seven days administration of esomeprazole increased the C_{max} and also shown significant increase in AUC of glipizide which indicate potential absorption profile of glipizide in both normal and diabetic condition. On metabolism and excretion, esomeprazole has shown significant increase in half life and decreases the K_{el} when compared with glipizide alone which indicates interaction occurred at metabolism and excretion site also. These data confirmed that concomitant administration of glipizide and esomeprazole might result in

pharmacokinetic interaction. The above results suggested that esomeprazole produces synergistic effect with glipizide because esomeprazole increased the plasma levels of glipizide in both normal and diabetic rats. The mechanism involved in this interaction may be the inhibition of CYP3A4 enzyme, the enzyme responsible for metabolizing glipizide by esomeprazole.

"Cite this article"

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