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**INDO AMERICAN
JOURNAL OF
PHARMACEUTICAL
RESEARCH**

Influence of Esomeprazole on the Pharmacokinetic and Pharmacodynamic Properties of Glipizide in Normal and Diabetic Guinea Pigs

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ARTICLE INFO

Article history

Received 15 Sep 2012
 Available 10 Oct online
 10/10/2012

Keywords

Glipizide,
 Esomeprazole,
 Alloxan,
 Pharmacokinetic,
 Pharmacodynamic.

ABSTRACT

The present work studied the influence of esomeprazole (Eso) on the pharmacokinetics (PK) and Pharmacodynamic (PD) of glipizide (Gli) in nondiabetic and diabetic animal models to evaluate the safety and effectiveness of the combination. Studies were conducted in normal and alloxan induced diabetic guinea pigs. Diabetes was induced by a single intraperitoneal injection of alloxan (200 mg/kg), and then glipizide and esomeprazole were administered orally for 7 days. On 8th day, the blood samples were collected at regular time intervals and the pharmacodynamic and pharmacokinetic parameters of glipizide, before and after esomeprazole treatment were determined. The blood glucose levels were estimated by Glucose Oxidase-Peroxidase (GOD-POD) method. Esomeprazole treatment has shown maximum antidiabetic effect at 6th hour after oral administration. Pretreatment with esomeprazole for seven days resulted in significant hypoglycemic effect of glipizide when compared with glipizide alone in both diabetic and normal animals. Esomeprazole has shown significant increase in pharmacokinetic profile of glipizide in both single and multiple days treatment. Present study results suggested that, esomeprazole significantly increases the concentration and AUC (area under curve) of glipizide due to inhibition of Cytochrome P-450 (CYP) enzyme. Hence, the present study indicated that esomeprazole has potential effect on pharmacokinetics and pharmacodynamics of glipizide.

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Please cite this article in press as Jaideep Singh et.al. Influence of Esomeprazole on the Pharmacokinetic and Pharmacodynamic Properties of Glipizide in Normal and Diabetic Guinea Pigs . Indo American Journal of Pharm. Research.2012;2(10).

INTRODUCTION

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus who have failed diet and exercise therapy and it appears to be the most effective insulin secretagogue both in first phase insulin secretion and in sustained stimulatory response during long term administration¹. Glipizide is extensively metabolized in the liver by CYP2C9² and CYP3A4^{3,4,5}. Proton pump inhibitors (PPI) are considered a major class of antiulcer drugs which are widely used in the treatment of acid-peptic diseases including gastroesophageal reflux disorder and peptic ulcer disease. These drugs have fewer side effects, few significant drug interactions and are considered safe for chronic treatment. Omeprazole, lansoprazole, rabeprazole and esomeprazole appear to have similar efficacy⁶. Esomeprazole, the (S)-isomer of omeprazole, is the first PPIs developed as a single isomer for the treatment of acid-peptic diseases. Esomeprazole is extensively metabolized by CYP3A4 and CYP2C19 isoenzyme in the liver⁷. Hence, both drugs are metabolized by same CYP enzyme, therefore the potential of drug interactions between these two groups of drugs exist. Moreover, the high incidence of gastrointestinal disorders and diabetes may imply the existence of one in the presence of the other. Diabetic patients may also be affected with many other diseases like peptic ulcer, hypertension and fungal infections, which require prolong treatment⁸. There are reports that several patients suffering from diabetes are prone to peptic ulcer infections⁹. In such cases, concomitant administration of antiulcer agent like omeprazole, pantoprazole, lansoprazole, ranitidine with antidiabetic agents is required. The drug interactions of glipizide and esomeprazole in these situations will be important to the practicing physician. So far, no significant interactions have been reported. Therefore, the present study was conducted to evaluate the influence of esomeprazole on the pharmacodynamics and pharmacokinetics of glipizide.

MATERIALS AND METHODS

Esomeprazole was purchased from Sigma–Aldrich Co, St Louis, MO, USA and glipizide was obtained as gift samples from Matrix Pvt. Ltd, Hyderabad.

Animals:

Study was conducted on guinea pigs of either sex, weight range 400-450 grams. Guinea pigs were kept under standard animal house conditions of 12 hours day-night cycle at a temperature of $25\pm 2^{\circ}\text{C}$ and humidity of $60\pm 2\%$. The animals were allowed to take water ad libitum and free access to standard diet.

Alloxan induced diabetes:

Diabetes mellitus was induced by alloxan 200 mg/kg i.p., to overnight fasted animals¹⁰. The animals showing blood glucose levels > 300 mg/dL, after seven days, were selected for the study.

Acute toxicity studies:

LD₅₀ of test compounds were performed as per the O.E.C.D guideline 423. The compounds were administered orally to groups of 6 animals. After administration of test compounds the guinea pig were observed for gross behavioral neurological autonomic and toxic effects. The toxicological effects were observed in terms of mortality. No death occurred within 24 hour of dose of 400 mcg/kg but at a dose more than 500 mcg/kg, 50% mortality was observed. As dose was increased further up to 600 mcg/kg, total mortality was found. Hence, 400 mcg/kg dose was considered as effective dose¹¹.

Experimental Procedure:

Pharmacokinetic study:

Guinea pigs were randomly distributed into four groups of six animals in each group. The animals in group-1 received vehicle, group-2 received esomeprazole (400 mcg/kg, p.o.), group-3 received esomeprazole followed by 1 hour after glipizide (5 mg/kg, p.o), single day interaction (SDI), group-4 guinea pigs were pretreated with

esomeprazole (400 mcg/kg, p.o.) for 7 days, on 8th day esomeprazole (400 mcg/kg, p.o.) followed by 1 hour after glipizide (5 mg/kg, p.o.), multiple day interaction (MDI). Blood samples (0.5ml) were collected at time intervals 0, 0.5, 1, 2, 4, 8, and 24 hour post dose. Each sample was collected in labeled, heparinized test tubes and centrifuged at 3000 rpm for 10 min. Plasma was separated by centrifugation and stored at -20°C until assayed for glipizide by high-performance liquid chromatography (HPLC) method.

Pharmacodynamic study:

Guinea pigs were randomly distributed into six groups of six animals in each group. Animals in group 1 and 2 are normal and diabetic control which received vehicle, group 3 and 4 are normal and diabetic control which received glipizide (5 mg/kg, p.o.) for 7 days, group 5 and 6 are normal and diabetic guinea pigs, were pretreated with esomeprazole (400 mcg/kg, p.o.) for 7 days, on 8th day esomeprazole (400 mcg/kg, p.o.) followed by 1 hour after glipizide (5 mg/kg, p.o.). The blood samples were collected at 0.0, 2.0, 4.0, 6.0, 8.0 and 24.0 hours after the administration of glipizide and analyzed for glucose levels by using the Accutrend Alpha Glucometer (Roche Diagnostics, Penzberg, Germany)¹².

Table 1: The pharmacokinetic parameters of glipizide before and during esomeprazole treatment in healthy animals.

Pharmacokinetic parameters	Glipizide	Glipizide+ Esomeprazole (SDI)	Glipizide+ Esomeprazole (MDI)
C _{max} (mcg/ml)	6.942 ± 0.43	8.204 ± 0.48**	11.2921 ± 0.58***
T _{max} (h)	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
AUC (0-24)	70.962 ± 5.2	100.511 ± 8.2**	142.238 ± 12.8***
K _{el} (h ⁻¹)	0.119 ± 0.018	0.047 ± 0.012***	0.053 ± 0.01***
T _{1/2} (h)	5.82 ± 0.21	7.84 ± 0.46*	9.05 ± 0.38**
MRT (h)	7.69 ± 0.23	9.28 ± 0.41	10.28 ± 0.97*

Mean ± SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to glipizide control. SDI (Single dose interaction), MDI (Multiple dose interaction)

Pharmacokinetic data analysis¹³:

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:

The results were expressed as mean±SEM. The significance was determined by applying one way ANOVA.

RESULTS

In the present study, the plasma glipizide levels and pharmacokinetic parameters of glipizide like AUC, half-life (T_{1/2}), K_{el}, C_{max}, and T_{max} were altered significantly with single- and multiple-dose treatments of esomeprazole in healthy guinea pigs and the results are shown in table 1 and figure 1 (Fig 1) respectively.

Multiple day treatment of esomeprazole has enhanced glucose lowering activity of glipizide in both normal and diabetic animals. The peak effect was observed at sixth hour. Concomitant administration of esomeprazole with glipizide increases percentage reduction in both normal (Gli+Eso, 49.2 ± 2.2 vs. Gli, 42.6 ± 5.3) and diabetic (Gli+Eso, 47.4 ± 0.8 vs. Gli, 42.4 ± 1.1) animals. Repeated dosing of esomeprazole enhanced the antidiabetic effect of glipizide in both normal and diabetic animals when compared with glipizide alone and the results are shown in Figure-2A and 2B.

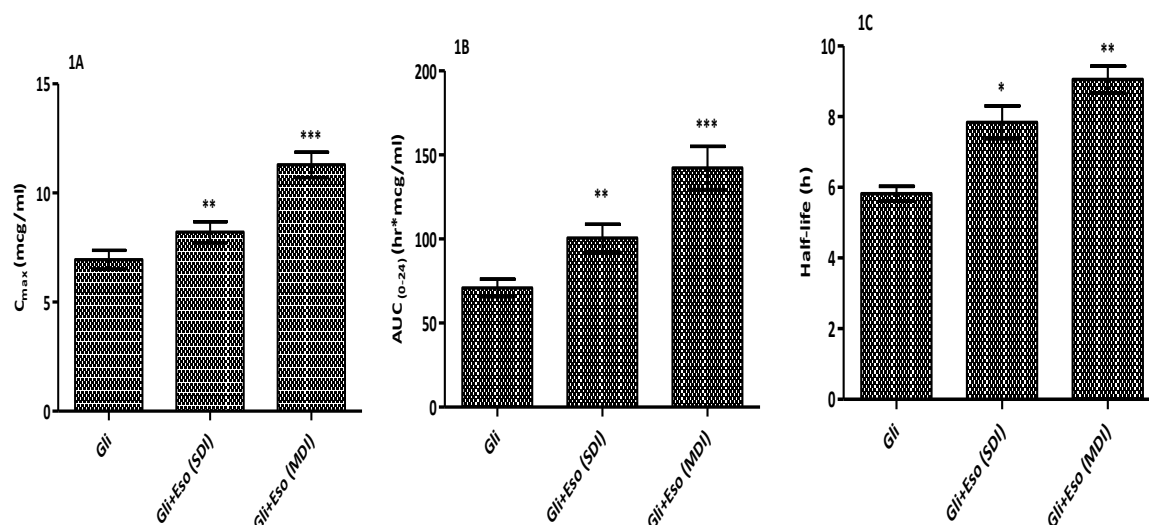


Fig. 1. The comparison of mean \pm SEM pharmacokinetic parameters (C_{max} -1A), (AUC-1B), (Half-life-1C) of glipizide (5 mg/kg) following pretreatment with esomeprazole (400 mcg/kg) by oral administration in healthy animals. SDI (Single dose interaction), MDI (Multiple dose interaction).

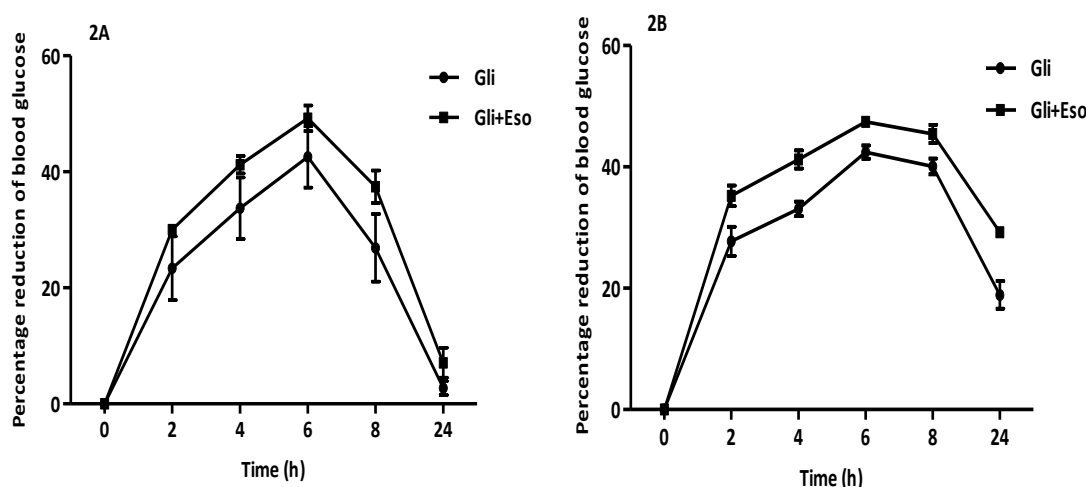


Fig. 2. The comparison of mean \pm SEM percentage reduction of blood glucose-time profile of glipizide (5 mg/kg) following pretreatment with esomeprazole (400 mcg/kg) by oral administration in healthy (Fig. 2A) and diabetic (Fig. 2B) animals.

DISCUSSION

The healthy animal model served to quickly identify the interaction. It is well established that glipizide acts by both pancreatic (insulin release by K^+ channel inhibition the cells) and extra pancreatic (tissue uptake of glucose) mechanisms. The target for sulphonyl urea activity is ATP sensitive K^+ channels (K^+ ATP channels). The sulphonylureas and related drugs used in type II diabetes stimulate insulin by closing K^+ ATP channels in pancreatic cells¹⁴. Esomeprazole is an antiulcer agent which is a proton pump inhibitor and esomeprazole is an S-isomer of omeprazole. Esomeprazole suppresses gastric acid secretion by specific inhibition of the H^+/K^+ ATPase in the gastric parietal cell. Thus, esomeprazole blocks the final step in acid production and hence reduces acidity¹⁵.

Single day administration of esomeprazole resulted in increased C_{max} and AUC of glipizide when compared with glipizide alone. Furthermore, the $T_{1/2}$, which reflects the elimination of glipizide, was also significantly altered by esomeprazole. These results suggest that the increased plasma concentrations of glipizide in esomeprazole treated animals would be caused by an increase in glipizide bioavailability.

In multiple dose interactions, the results showed that the multiple days administration of esomeprazole increased the glucose lowering effect of glipizide in both normal and diabetic guinea pigs. The repeated administration of esomeprazole significantly increased the C_{max} and AUC of glipizide. Multiple days treatment of esomeprazole further increased the $T_{1/2}$ of glipizide in normal animals when compared with glipizide alone.

Both single and multiple days treatment of esomeprazole increased AUC and C_{max} which indicated the interaction occur at absorption site and increase in half-life resulted in interaction occur at metabolism site. These data confirmed that concomitant administration of glipizide and esomeprazole might result in pharmacokinetic interaction. However, the antidiabetic activity of glipizide was enhanced by esomeprazole, following multiple dose treatment and this may be evidence the presence of potential interaction between glipizide and esomeprazole. The above results suggested that esomeprazole produces synergistic effect with glipizide because it is having antidiabetic effect in both healthy and diabetic animals. The mechanism involved in this interaction may be the inhibition of CYP3A4 enzyme, the enzyme responsible for metabolizing glipizide by esomeprazole.

CONCLUSION

The interaction observed appears to be pharmacokinetic interaction at absorption, metabolism and excretion site and also at pharmacodynamics level.

REFERENCES

1. Verma RK, Garg S. Development and evaluation of osmotically sustained oral drug delivery systems of glipizide. Eur. J.pharm. Biopharm. 2004;57:513-525.
2. Kidd RS, Straugh AB, Meyer MC, [Blaisdell J](#), [Goldstein JA](#), [Dalton JT](#). Pharmacokinetics of chlorpheniramine, phenytoin, glipizide and nifedipine in an individual homozygous for the CYP2C9*3 allele. Pharmacogenetics. 1999;9:71-80.
3. Peart GF, Boutagy J, Shenfield GM. The metabolism of glyburide in subjects of known debrisoquin phenotype. Clin Pharm Ther. 1989;20:283-95.
4. Wensing G. Glipizide: an oral hypoglycemic drug. Am J Med Sci. 1989;298:69-71.
5. Brian WR. Hypoglycemic agents, In: Levy RH, Thummel KE, Tranger WF, Haunsten PD, Eichelbaum M et al. Metabolic drug interactions. Philadelphia: Lippincott Williams & Wilkins; 2000.
6. Spancer CM, Diana Faulds. Esomeprazole. Drugs. 2000;60:321-329
7. Andersson T, Hassan-Alin M, Hasselgren G, Röhss K. Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. ClinPharmacokinet. 2001;40:523-37.
8. Suresh J, Ramchandra SS, Kharya MD. Influence of Itraconazole on antidiabetic effect of Thiazolidinedione in diabetic rats. Int J pharma and pharmaceutical science. 2009;1:119-124.
9. Lai KC, Lam SK, Chu KM. Lansoprazole for the prevention of recurrences of ulcer complications form long-term low-dose aspirin use. N Eng J Med. 2002;346:2033-38.
10. Elena M, Ottavio G. Proposal open for discussion: defining agreed diagnostic procedures in experimental diabetes. J Ethnopharmacol. 2008;115(2):163-172.
11. Rahul Hajare¹, Darvhekar VM, AshishShewale, Vijay Patil. Evaluation of antihistaminic activity of Piper betel leaf in guinea pig. African Journal of Pharmacy and Pharmacology. 2011;5(2):113-117.
12. Lahoti SR, Puranik PK, Heda AA, Navale RB, Battase AB, Une HD. Comparative pharmacokinetic and pharmacodynamic evaluation of glipizide after oral and transdermal administration. Journal of Pharmacy Research. 2010;3(12):3109-3112.
13. Prashanth S, Anil Kumar A, Madhu B, Rama N, VidyaSagar J. Pharmacokinetic and pharmacodynamic drug interactions of carbamazepine and glibenclamide in healthy albino wistar rats. J PharmacolPharmacother. 2011;2(1):7-10.
14. Henrik DR, Brekardine, Uhde I, Schwanstecher C, Schwanstecher M. Stoichiometry of Sulfonylurea-Induced ATP-Sensitive Potassium Channel Closure. Molecular Pharmacology. 1999;55:1060-1066.
15. [Malfetheriner P](#), [Chan F](#), [EL McColl](#) K. Peptic ulcer disease. The Lancet. 2009;374:1449-1461.



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