Vol 1|Issue 1| 2011 |4-6.

ISSN 2248 - 9169
Print ISSN 2248 - 9150

International Journal of
Experimental Pharmacology

www.ijepjournal.com

DRUG INTERACTION OF OMEPRAZOLE ON SULFONYLUREAS IN DIABETIC RATS

***J. Uma Maheswari, R. Gandhimathi**

[*]Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, Sree Sainathnagar, Chandragiri (M), Tirupati, Andhra Pradesh, India-517102.

ABSTRACT

The influence of larger dose of pretreatment for seven days on the anti diabetic effect of glibenclamide and glipizide was studied. This study was conducted on alloxan induced diabetic rats of either sex, randomly distributed into 4 different groups. The first two groups were treated with acacia suspension 2%w/v and omeprazole 20 mg/kg, p.o in 2% w/v gum acacia suspension for seven days and the other two groups (3 and 4) were treated with glibenclamide and glipizide respectively. The animals of the same groups were pretreated with omeprazole (20 mg/kg) for 7 days. On eighth day, glibenclamide (200 µg/kg, p.o) and glipizide (200 µg/kg, p.o) were administered to respective groups one hour after treatment. Blood samples were collected from retro-orbital sinus at time intervals of 00, 1, 2, 4, 8, 12, 18, and 24 hrs and plasma glucose levels were estimated by GOD/POD method. The onset of glucose reduction, peak effect and duration of action were assessed. The study indicated that higher dose (around 8 times of therapeutic dose) of omeprazole pretreatment has enhanced the anti diabetic effect of glibenclamide and glipizide significantly. Hence it is suggested that there is no possibility of occurrence of drug interaction during the concomitant usage of therapeutic doses of omeprazole and sulfonylureas. Therefore the therapeutic drug monitoring and readjustment of the dose and frequency of administration of sulfonylureas are not essential at therapeutic dose levels.

Key words: Omeprazole, Glibenclamide, Glipizide, Alloxan, Antidiabetic activity.

INTRODUCTION

There are several incidences that a patient may suffer with more than one disease at a time. It is a need to treat all his ailments simultaneously. Hence it may require administering more than one drug at a time. In such instances, the potential for drug interactions is therefore substantial and polypharmacy is an important factor to be considered when prescribing for a prolonged period. According to reports, the risk of drug interaction increases exponentially with the no of drugs given to a patient [1]. It is the fourth to sixth leading cause for death in United States [2]. Diabetes mellitus is a disease characterized by elevated blood glucose levels and requires treatment for lifelong. Diabetic patients may also be affected with many other diseases like peptic ulcer, fungal infections and hypertension. All these diseases are also require treatment for chronic period/ life-time. The reports reveal that about 7% of diabetic patients are suffering from peptic ulcers [3]. There are several patients who are suffering with both diabetes and peptic ulcer. In such patients proton pump inhibitors like omeprazole, and sulfonylureas like glibenclamide and glipizide were administered concomitantly. There are reports that omeprazole is known to inhibit cytochrome P-450 enzyme system [4], hence there is a possibility of occurrence of pharmacokinetic type of drug interactions with concomitantly used drugs. Glibenclamide and glipizide are metabolized by cytochrome P-450 enzyme system [5, 6]. Therefore the present study was conducted in diabetic rats to assess the

Corresponding Author

J. Uma Maheswari
E mail: umamahes_jdu@yahoo.co.in

ISSN 2248 - 9169
Print ISSN 2248 - 9150

influence of omeprazole pretreatment on the anti diabetic effects of sulfonylureas like glibenclamide and glipizide.

MATERIALS AND METHODS

Animals

The study was conducted on diabetic rats (wistar strain) of either sex weighing 200-260 g. The animals were randomly distributed into 4 groups of 6 animals each. The albino rats were procured from Sri Venkateshwara Enterprises, Bangalore. The animals were housed under ambient temperature of 28 ± 2ºC and 50 ± 2% relative humidity with 12 hr light / 12 hr dark cycle. The study was conducted in Sree Vidyanikethan College of Pharmacy, Sree Sainathnagar, Chandragiri (M), Tirupati, Andhra Pradesh, India-517102.

Drugs

Glibenclamide and glipizide were obtained from Cipla, Mumbai and omeprazole was obtained from Dr. Reddy's labs ltd. Hyderabad. Glibenclamide (200 µg/kg, p.o), glipizide (200 µg/kg, p.o) and omeprazole (20 mg/kg, p.o for 7 days) suspensions were prepared by using 2% w/v gum acacia as a suspending agent.

Experimental

Induction of diabetes in rats

Diabetes was induced in the rats by administering 120 mg/kg of Alloxan intraperitoneally into the 24 hr fasted rats [7]. Blood samples were collected after 24 hrs and blood glucose levels were estimated. Albino rats which have shown more than 200 mg/dl blood glucose levels were considered as diabetic. The blood glucose levels were monitored for further four days. From this it was confirmed that diabetes was induced in 24 hrs and stabilized within 4 days. These animals were used for further studies.

The diabetic rats were marked conveniently and randomly distributed into four groups of 6 animals each. All the animals were over night fasted with water *ad libitum*. The animals in group-1 received 2% w/v acacia suspension and the animals in the group- 2 received omeprazole (20 mg/kg, p.o) in acacia suspension. Group-3 received glibenclamide (200 µg/kg, p.o) and group-4 received glipizide (200 µg/kg, p.o). Blood samples were collected at 0.0, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0, 24.0 hr after treatment by retro-orbital sinus in mild anaesthetized rats. Blood glucose levels were estimated by GOD/POD method8 and expressed as mg/100 ml of blood. In the next phase of the experiment, the animals of group-3 and 4 received omeprazole 20 mg/kg, p.o for seven days. On the 7th day, 6 hours after administration of omeprazole, the animals were fasted for 14 hours. On the 8th day, omeprazole was given as usual. One hour after the treatment, animals of group-3 received glibenclamide 200 µg/kg, p.o and group-4 received glipizide 200µg/kg, p.o. Blood samples were collected thereafter at above mentioned intervals and glucose levels were estimated. The % blood glucose reduction at various time intervals were calculated and compiled in Table 1.

Statistical analysis

The data was analyzed by Student Newman kleus test. P values lower than 0.05 were considered as statistically significant.

RESULTS

It is evident from the table 1 that, treatment with acacia suspension alone has not influenced the blood glucose levels in diabetic rats. Omeprazole *perse* did not alter the blood glucose levels. However, pretreatment with omeprazole 20 mg/kg, p.o has not significantly altered the onset of antidiabetic effect of glibenclamide and significantly enhanced peak antidiabetic effect from 41.11 ± 3.11 at 4th hr to 58.76 ± 2.19 at 4th hr and duration of antidiabetic effect was raised from 17 hrs to 23 hrs. Whereas pre-treatment with omeprazole 20 mg/kg, p.o has significantly altered the onset of antidiabetic effect of glipizide and enhanced the peak antidiabetic effect from 37.58 ± 1.48 to 48.61 ± 1.03 at 2nd hr. Duration of antidiabetic effect was slightly altered.

Table No. 1 Percentage decrease in blood glucose levels at different time intervals (Following various treatments in diabetic albino rats)

Time in Hrs	Acacia suspension	Omeprazole (20 mg/kg, p.o,)	Glibenclamide (200 µg/kg, p.o,)	Omeprazole (20 mg/kg, p.o, 7 days)+Glibenclamide (200 µg/kg, p.o,)	Glipizide (200 µg/kg, p.o,)	Omeprazole (20 mg/kg, p.o, 7 days) +Glipizide (200 µg/kg, p.o,)
Fasting	-	-	-	-	-	-
1.0	-2.14 ± 1.05	0.22 ± 1.42	21.12 ± 5.46	20.72 ± 3.16	14.58 ± 2.44	24.19 ± 1.03**
2.0	0.73 ± 0.45	-0.25 ± 0.49	37.16 ± 6.48	48.79 ± 3.15	37.58 ± 1.48	48.61 ± 1.03**
4.0	-7.27 ± 7.28	-3.27 ± 1.49	41.11 ± 3.11	58.76 ± 2.19*	35.59 ± 1.49	48.41 ± 3.17*
8.0	-0.55 ± 1.44	-3.25 ± 2.41	36.11 ± 2.14	57.73 ± 2.15**	33.53 ± 1.42	35.13 ± 3.01
12.0	-0.14 ± 0.59	-1.02 ± 2.43	28.19 ± 1.17	52.79 ± 3.13***	25.56 ± 1.42	23.14 ± 1.05
18.0	-1.49 ± 0.77	2.23 ± 1.41	20.16 ± 1.14	43.37± 3.71***	16.51 ± 1.46	17.02 ± 1.08
24.0	0.47 ± 1.43	0.29 ± 1.44	7.15 ± 2.15	30.79 ± 2.41***	7.64 ± 0.74	8.16 ± 1.19

*n=6. * Significant at p< 0.05; ** highly significant at p<0.01; *** very highly significant at* p<0.001

ISSN 2248 - 9169
Print ISSN 2248 - 9150

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder which requires treatment for life long. Peptic ulcer is one such disease which requires treatment for a prolonged period. If a patient is suffering with diabetes mellitus and peptic ulcer, we may have to use anti diabetic drugs such as sulfonylureas like glibenclamide and glipizide and proton pump inhibitors like omeprazole. In such situations, there is a possibility of occurrence of drug interactions. Our pilot study has indicated that drug interactions do not occur when omeprazole and glibenclamide/glipizide is administered concomitantly at therapeutic doses [8]. Attempts were made to assess the influence of higher doses of omeprazole on anti diabetic effect of sulfonylureas. It was observed that 8 times that of the therapeutic dose required to significantly altering the effects of sulfonylureas. For the assessment of the potentiation of anti diabetic effect, onset of action, (time taken to reduce minimum of 20% reduction in blood glucose levels), peak effect, duration of anti diabetic effect (duration in which minimum of 20% reduction in blood glucose levels are maintained) were considered.

Since omeprazole (20 mg/kg) *perse* did not influenced the blood glucose levels and the possibility of occurrence of pharmacodynamic interaction can be ruled out. In our study, pretreatment with omeprazole did not alter the onset of action of glibenclamide. However, peak effect and duration of anti diabetic effect induced by glibenclamide is significantly enhanced. In case of pretreatment with omeprazole the onset, peak effect and duration of action of glipizide were increased significantly. These findings suggest that omeprazole may interfere with the absorption of glipizide. It may be inferred from the results that omeprazole has retarded their metabolism by inhibiting the enzymes responsible for their metabolism. There are reports that both glibenclamide and glipizide are mainly metabolized by CYP2C9 and CYP3A4 [9-13]. Reports also indicate that omeprazole is having lower affinity for cytochrome P 450 system [14]. It is evident from the results that 8 times the therapeutic dose of omeprazole enhanced the anti diabetic effect of both the sulfonylureas. This may be due to weak inhibitory effect of omeprazole on CYP2C9 and CYP3A4. Further studies are undertaken to establish the influence of omeprazole pretreatment on the pharmacokinetic parameters of sulfonylureas.

CONCLUSION

Since 8 times of therapeutic dose of omeprazole has influenced the anti diabetic effect of sulfonylureas, it may be concluded that during the concomitant administration of sulfonylureas and omeprazole at therapeutic doses, the dose and frequency of administration of sulfonylureas need not be readjusted.

REFERENCES

1. Kohler GI, Bode-Boger SM, Busse R, et al. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. *Int J Clin Pharmacol Ther*., 38, 2000, 504-613.
2. Yuan R, Parmelee T, Balian JD, et al. In vitro studies; experience of the food and drug administration. *Clin Pharmacol Ther*., 66, 1999, 9-15.
3. Burghen GA, Murrell LR, Whitington GL, Klyce MK, Burstein S. Acid peptic diseases in children with type-I diabetes mellitus. A complicating relationship. *Am J Dis Child*., 146 (6), 1992, 718-22.
4. Joyce A.Golstein, Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Brit Clin Pharmacol.,* 52 (4), 2001, 349.
5. Islam SI, Masuda QN, Bolaji OO, Shaheen FM, Sheikh IA. Possible interaction between cyclosporine and glibenclamide in post transplant diabetic pateints. *Therapeutic Drug Monitorung*, 18(5), 1996, 624-626.
6. Mikko Niemi, Janne T. Backman, Mikko Neuvonen, et al. Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. *Clin Pharmacol Ther.,* 69 (6), 2001, 400-406.
7. Ghosh MN. Fundamentals of Experimental Pharmacology, 2nd ed. Scientific book agency, Calcutta. 1975, 191.
8. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen reptor. *Ann Clin Biochem.,* 6, 1969, 24-7.
9. Peart GF, Boutagy J, Shenfield GM. The metabolism of glyburide in subjects of known debrisoquin phenotype. *Clin Pharm Ther.*, 20, 1989, 283-95.
10. Rydberg T, Jonsson A, Karlsson MO, Melander A. Concentration-effect relations of glibenclamide and its active metabolites in man: modeling of Pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol.,* 43, 1997, 373-81.
11. Wensing G.Glipizide: an oral hypoglycemic drug. *Am J Med Sci.,* 298, 1989, 69-71.
12. Brian WR. Hypoglycemic agents, In: Levy RH, Thummel KE, Tranger WF, Haunsten PD, Eichelbaum M, eds.
13. Metabolic drug interactions. Philadelphia: Lippincott Williams & Wilkins. 2000, 429-43.
14. Kidd RS, Straughn AB, Meyer MC, et al. Pharmacokinetics of chlorpheniramine, phenytoin, glipizide and nifedipine in an individual homozygous for the CYP2C9*3 allele. *Pharmacogenetics*, 9, 1999, 71-80.
15. Steinijans VW, Huber R, Hartmann M, Bliesath H, Wurst W, Radtke HW. Lack of omeprazole drug interactions in man. *Int J Clin Pharmacol Ther.,* 36 (10), 1998, 521-4.