



POSSIBLE OCCURRENCE OF DRUG INTERACTION BETWEEN FLUOXETINE AND GLIMEPIRIDE IN TWO DISSIMILAR SPECIES

Vijay Kamat^{1*}, Neelam Raj², Pramod N³, Rajendra S V¹

¹Department of Pharmacology, SCS College of Pharmacy, Harapanahalli-583131, Karnataka, India.

²Department of Pharmacology Pulla Reddy Institute of Pharmacy, Annaram, Medak, Andhra Pradesh, India.

³Department of Pharmaceutical chemistry, A.M. Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India.

ABSTRACT

The aim of the study is to investigate the effects of fluoxetine pretreatment for 7 days on the hypoglycemic/antidiabetic activity of glimepiride in rats (normal and diabetic) and rabbits. Normal rats, alloxan induced diabetic rats, and normal rabbits of either sex, randomly distributed into required groups. Fluoxetine per se was carried out in the first part of the investigation. The hypoglycemic/antidiabetic activity was carried out in the next part of the investigation and then in the final phase, fluoxetine was administered for 7 consecutive days and on 8th day, one hour after the administration of fluoxetine, glimepiride was administered. Blood samples were collected from retro orbital sinus of rats and from marginal ear vein of rabbits at different intervals up to 24h and were analyzed for blood glucose concentrations by GOD/POD method. Onset, peak and duration of hypoglycemia were used as parameters of the investigation. Fluoxetine per se did not alter the blood glucose levels in both rats and rabbits. However, pretreatment with fluoxetine potentiated the peak and duration of hypoglycemia induced by glimepiride in normal/diabetic rats and rabbits. Hence, it is inferred that there is every possibility of occurrence of drug interactions during concomitant usage of therapeutic doses of fluoxetine and glimepiride. Therefore, therapeutic monitoring may be required to avoid the possibility of complications of severe hypoglycemia.

Key words: Fluoxetine, Glimepiride, Alloxan, Antidiabetic activity.

INTRODUCTION

Drug interaction occurs when effects of one drug is modified by the presence of another drug, food, drink or environmental chemical agents. The prevalence of potential clinically important drug-drug interactions varies tremendously and is prevailed to an extent of 4.7%-88% (Alexandra Elisabeth RB *et al.*, 2004). In poly pharmacy, it is important to determine the incidence and frequency of occurrence of drug interactions with serious implications in hospitalized patients. In addition, it is also

important to find out agents that are most likely to produce hazardous interactions (Sunilkumar B *et al.*, 1998). The importance of antidepressants as inhibitors of metabolic enzymes is underscored by the fact that the majority of patients taking antidepressants are taking at least one other prescription drug and from one third to two thirds are taking three or more drugs in addition to their antidepressants (Rene HL *et al.*, 2000).

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels requires lifelong treatment (Suresh Janadri *et al.*, 2009). The WHO estimates that depression occurs at much higher rates (15-25%) in diabetic patients than in the general populations even though depression symptoms are frequently under diagnosed. More often, depression may be a risk factor

Corresponding Author

Vijay Kamat

Email: kamatvijay23@gmail.com

for diabetes type 2 due to its effects upon diet, exercise, smoking or drinking. Treatment with anti-depressants for diabetic individuals must consider the variability in blood glucose level control at different times and a comparison of the available antidepressant agents is always recommended (Chitra VV *et al.*, 2009). The capacity of selective serotonin reuptake inhibitors (SSRIs) to inhibit the metabolic activity of cytochrome P450 isoenzyme system has spurred over a decade of intense psychopharmacological and pharmacogenetic research. Fluoxetine is the parent drug of the SSRI (selective serotonin reuptake inhibitor) antidepressant class and is still one of the most highly used drugs of this class worldwide for the treatment of major depression, bulimia nervosa, panic attacks and obsessive compulsive disorders. There are reports that fluoxetine is a modest inhibitor of CYP3A4 and CYP2C9 (Sheila RB *et al.*, 2001; Mandrioli R *et al.*, 2006). Glimepiride is a second generation sulfonylurea antidiabetic agent, lowers blood glucose primarily by stimulating the release of insulin from functioning pancreatic beta-cells. Glimepiride metabolism is mediated by CYP2C9 (Aziz Karim *et al.*, 2008). Hence there is a possibility of occurrence of pharmacokinetic type of drug interactions when fluoxetine is concomitantly administered with glimepiride. Therefore the present study was conducted on normal/diabetic rats and rabbits to assess the influence of fluoxetine pretreatment on the hypoglycemic effects of sulfonylureas like glimepiride.

MATERIALS AND METHODS

Animals

The study was conducted in albino wistar rats of either sex, weight range 150-300 gm were suitably divided in 3 groups of 6 rats in each. Also, normal albino rabbits of either sex weighing 1.5-2.0 kg were recruited for the study and they were divided into 2 groups of 4 animals in each. The animals were procured from Sri Venkateshwara Enterprises, Bengaluru. They were housed under standard conditions (temperature of $28 \pm 2^\circ\text{C}$ and $50 \pm 2\%$ relative humidity with 12 hr light / dark cycle) and provided with water *ad libitum*. Prior approval by institutional ethics committee (reg. no: 157/99/CPCSEA) was obtained for conduction of experiments. The study was conducted in the PG Department of pharmacology of S.C.S. College of Pharmacy, Harapanahalli between 2010 and 2011.

Drugs

Fluoxetine and Glimepiride were provided as gift samples by Microlabs Ltd. (Bengaluru, India) and Karnataka Antibiotics and Pharmaceuticals Ltd. (Bengaluru, India) respectively.

Experimental Induction of diabetes mellitus

Diabetes was induced in rats by the administration of alloxan monohydrate in two doses, i.e. 100mg/kg and 50 mg/kg b.d.wt intraperitoneally for two consecutive days (Heikkila RE *et al.*, 1977). After 72 h, samples were collected from rats by orbital puncture of all surviving rats and serum was analysed for glucose levels. Rats which have shown more than 200 mg/dl blood glucose levels were considered as diabetic. The blood glucose levels were monitored for further three days. From this it was confirmed that diabetes was induced in 24 h and stabilized within 3 days. These animals were used for further studies.

Procedure

The study was conducted in 3 phases. In the first phase of the study, normal rats were used to assess the per se effect of fluoxetine (5.4 mg/kg p.o) on the blood glucose levels. In the second phase of the study, hypoglycemic activity was conducted using glimepiride alone (400µg/kg p.o) in acacia suspension. The blood sample were collected from retro-orbital sinus of rats at 0,1,2,4,8,12,18 and 24 h and blood glucose levels were estimated by GOD-POD method (Sheila RB *et al.*, 2001; Mandrioli R *et al.*, 2006). In the next part of the second phase, the animals were treated with fluoxetine (5.4 mg/kg p.o) consecutively for 7 days and on 8th day, one hour after the administration of fluoxetine (5.4 mg/kg), glimepiride was administered. Then the blood glucose levels were determined at frequent intervals of time up to 24 hours. Similar studies were also conducted in alloxan induced diabetic rats to verify the effects of fluoxetine on the hypoglycemia induced by glimepiride in pathophysiological conditions. In the third phase of the study, it was planned to use normal rabbits to verify the findings observed in rats. Furthermore, it was mandatory to use two dissimilar species for assessing the drug interaction at preclinical studies.

Statistical analysis

Data were expressed as mean \pm SEM (standard error of mean). The significance was determined by ANOVA followed by Dunnett's test. $P < 0.05$ is considered statistically significant.

It is clear from the table 1 and 2 that treatment with fluoxetine alone did not alter the blood glucose levels in normal rats and rabbits. Pretreatment with fluoxetine 5.4 mg/kg, p.o. has not altered the onset of hypoglycaemia induced by glimepiride. However peak hypoglycemia was shifted from $36.98 \pm 3.38\%$ at 4th h to $49.64 \pm 1.44\%$ at 8th h and duration of hypoglycaemia was raised from 16 h to 22 h in normal rats. Similarly in diabetic rats, pretreatment with fluoxetine 5.4 mg/kg, p.o increased the peak effect from $43.07 \pm 2.23\%$ to $51.02 \pm 1.55\%$. However onset and duration of

antidiabetic effect was not significantly altered in diabetic rats.

It was observed from table 2 that in case of

rabbits the peak hypoglycaemic effect was enhanced from 43.3±7.78% to 50.14±2.55%. However, onset and duration were not altered significantly.

RESULTS

Table 1. Percentage blood glucose reduction in normal albino rats and diabetic albino rats

S.No	Time in hr	Percentage blood glucose reduction in normal albino rats			Percentage blood glucose reduction in diabetic albino rats	
		Fluoxetine Per sec 5.4 mg/kg (Mean±SEM)	Glimepiride 400µg/kg (Mean±SEM)	Glimepiride+ Fluoxetine 400 µg/kg 5.4 mg/kg (Mean±SEM)	Glimepiride 400 µg/kg (Mean±SEM)	Glimepiride(400 µg /kg)+ Fluoxetine(5.4 mg/kg) (Mean±SEM)
1.	Fasting	---	---	---	---	---
2.	1.0	2.18±1.67	7.00±1.07	7.30±1.35	5.44±1.39	7.23±1.72
3.	2.0	0.44±2.41	16.73±1.77	22.15±0.54*	24.64±2.57	21.58±2.41
4.	4.0	1.27±1.64	36.98±3.38	38.16±2.38	43.07±2.23	50.21±1.80*
5.	8.0	0.25±2.64	30.81±3.41	49.64±1.44***	38.72±2.32	51.02±1.55**
6.	12.0	-1.52±2.44	22.21±2.44	42.79±2.39***	31.30±2.09	42.30±2.04**
7.	18.0	2.26±2.57	15.93±1.53	31.85±2.81***	22.48±1.97	36.72±2.36***
8.	24.0	-1.32±3.02	8.27±1.60	25.44±1.95***	15.27±1.72	29.57±2.36***

Table 2. Percentage blood glucose reduction in normal albino rabbits

S.No	Time in hr	Percentage blood glucose reduction in normal albino rabbits		
		Fluoxetine Per sec 5.4 mg/kg (Mean±SEM)	Glimepiride 200µg/kg (Mean±SEM)	Glimepiride (200 µg/kg)+ Fluoxetine (5.4 mg/kg) (Mean±SEM)
1.	Fasting	---	---	---
2.	1.0	-1.58±3.70	10.10±4.96	6.93±1.27
3.	2.0	-1.32±5.40	21.16±6.24	25.15±2.44
4.	4.0	3.79±1.83	43.30±7.78	50.14±2.55
5.	8.0	-0.86±2.64	32.67±2.13	45.37±1.18**
6.	12.0	0.36±1.15	26.61±3.09	38.93±0.99*
7.	18.0	1.96±6.40	14.39±1.23	23.93±1.45**
8.	24.0	5.36±0.89	8.33±3.17	20.1±0.64*

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder requiring lifelong treatment and the blood glucose levels will be controlled by antidiabetic drugs including glimepiride. Depression is a psychological disorder which also requires treatment for a specified/prolonged period and can be promptly treated with SSRIs including fluoxetine. If a patient is suffering with both these disorders/ diseases require simultaneous treatment with the aforementioned drugs for a specified period /chronic period.

In the first phase per se effect was carried with fluoxetine to determine the effects of it on the blood glucose levels. It was obvious from the obtained results that fluoxetine alone did not influence the blood glucose levels and hence the possibility of additive effect with sulfonylurea like glimepiride can be ruled out. For the assessment of the potentiation of hypoglycaemic/

antidiabetic effect, onset of action, (time taken to reduce minimum of 15% reduction in blood glucose levels), peak effect (maximum blood glucose reduction), duration of hypoglycemic/anti diabetic effect (duration in which minimum of 15 % reduction in blood glucose levels were maintained) were considered. In our study, it was observed that onset of action was not altered by pretreatment with fluoxetine and hence it may be inferred here that fluoxetine did not affect the absorption of glimepiride. However, pretreatment with fluoxetine (5.4 mg/kg) altered the peak effect and duration of hypoglycemia induced by glimepiride. It was indicated in the literature that glimepiride is a substrate for Cytochrome P450 2C9 and further fluoxetine is an inhibitor of CYP2D6, CYP2C8/2C9 and CYP 2C19 (Railey *et al.*, 1969; Trinder *et al.*, 1960). Hence it is hypothesized that fluoxetine influences the hypoglycemia induced by glimepiride by inhibiting the enzymes

involved in the metabolism. Our studies in normal/diabetic rats and normal rabbits suggested that drug interaction occurs between fluoxetine and glimepiride when they are used concurrently in normal and pathophysiological conditions like diabetes mellitus. Further studies may be required to establish the influence of repeated administration of fluoxetine on the pharmacokinetic parameters of glimepiride.

CONCLUSION

It may be concluded that during simultaneous administration of fluoxetine and glimepiride, the adjustment of dose and frequency of administration of glimepiride may be needed. Even it may be required to

monitor the blood glucose levels as a precautionary measure so as to avoid the complications of severe hypoglycemia.

ACKNOWLEDGEMENT

The authors are thankful to Sri.Sha.Bra. Chandramouleeshwara Swamiji, the President and Sri. T.M. Chandrashekharaiiah, the Secretary, T.M.A.E Society through principal S.C.S College of Pharmacy, harapanahalli, Karnataka, India for providing all the facilities to carry out this research work. We also thank Micro labs (Bengaluru) for providing fluoxetine and KAPL (Bengaluru) for providing glimepiride as gift samples.

REFERENCES

- Alexandra Elisabeth RB. Importance of drug-drug interaction in drug safety. Inaugural dissertation, *Universitat Basel*. 1, 2004, 8.
- Aziz Karim, Zhen Zhao, Margaret S. Replicate study design in bioequivalency assessment, pros and cons: bioavailabilities of the antidiabetic drugs pioglitazone and glimepiride present in a fixed-dose combination formulation. *J Clin Pharmacol*, 47, 2007, 806.
- Bo Tan, Yi-Fan Zhang et al. The effect of cyp 2C9 and 2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of glipizide in Chinese subjects, *Eur J Clin Pharmacol*, 2009.
- Chitra VV, Jaya Shankar Reddy, Mastan rao Y, Bhargavi Ch. Effect of fluoxetine and escitalopram on hypoglycaemic response of repaglinide. *Der Pharmacia Lettre*, 1 (1), 2009, 150-156.
- Ereshefsky L, Riesenman C, Lam YW. Antidepressant drug interactions and the cytochrome P450
- Heikkila RE. The prevention of alloxan-induced diabetes in mice by dimethyl sulfoxide. *Eur.J.Pharmacol*, 44, 1977, 191-193.
- Mandrioli R, Forti GC and Raggi MA. Fluoxetine Metabolism and Pharmacological Interactions: The role of cytochrome P450. *Current Drug Metabolism*, 7, 2006, 127-133.
- Railey. Adaptation of orbital bleeding technique to rapid serial blood studies. *Proc.Soc.Exp.Biol.Med*. 104, 1960, 751-754.
- Rene HL. Metabolic drug interactions, *Lippincott Williams and Wilkins*, 1, 2000, 529.
- Renee RK. Oral Antidiabetic Agents: A Comparative Review. *Journal of Pharmacy Practice*, 17, 2004, 39.
- Sheila RB and Cara A, Antidepressant Drug Interactions. *Journal of Pharmacy Practice*, 14, 2001, 467.
- Sunilkumar B, Lucia P, Miglani BD. Possible drug interactions in hospitalized patients. *The Ind J Hos Pharm*, 1998, 91-93.
- SureshJanadri, Ramachandra SS, Kharya MD. Influence of itraconazole on antidiabetic effect of thiazolidinedione in diabetic rats. *International Journal of Pharmacy and Pharmaceutical Sciences*, 1(1), 2009, 1-8.
- System. The role of cytochrome P450 2D6. *Clin Pharmacokinet*, 29(10), 1995, 10-8.
- Tom Lynch, Amy Price. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *American Family Physician*, 76(3), 2007, 391-95.
- Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen reprot. *Ann Clin Biochem*, 6, 1969, 24-7.